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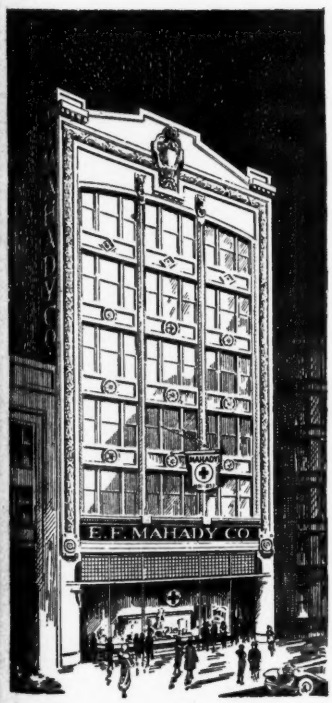

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The Massachusetts Medical Society

The next Annual Meeting of the Massachusetts Medical Society will be held in Worcester, at the Hotel Bancroft, Monday, Tuesday and Wednesday, June 4-5-6, 1934.

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CANCER OF THE STOMACH

BY FRANK H. LAHEY, M.D.,* AND SARA M. JORDAN, M.D.*

IT is a grim paradox that the most serious disease of the stomach, carcinoma, is usually the least blatant in its onset. While the benign ulcer makes its appearance with very definite symptoms, sometimes even with the dramatic symptoms of hemorrhage or perforation, and with a fully developed x-ray deformity which Cole states has its full size when first seen and has never been known to grow larger under observation, the malignant lesions of the stomach, especially the carcinoma, are characterized by an insidious inception which is often considered clinically negligible.

This early clinically latent period of the disease, as in cancer of all organs, is, of course, the stage at which its detection offers an opportunity for the greatest chance of safety from recurrence, and with this fact in mind, the internist, the radiologist, and the surgeon are united in a very serious effort to diagnose and treat the lesion at this incipient stage.

There are three types of data which have informatory value in the diagnosis of cancer of the stomach after it has passed beyond the incipient into the well-developed stage. These may be briefly summarized as follows: first, the history of loss of appetite, loss of weight, and epigastric distress; secondly, the physical examination which shows a pale individual with evident recent loss of weight, and with a mass in the epigastrium or left upper quadrant; and finally, the laboratory data demonstrating an achlorhydria or a hypochlorhydria, an anemia, occult blood in the stools, and radiologically, a distorted contour of the stomach. When a combination of these three types of diagnostic data is presented, there remains no doubt as to the diagnosis, and the only matter to be decided is the operability of the lesion. Such a lesion has developed far beyond the quiescent stage of inception.

The earlier stage, unlike the later unmistakably obvious one, shows symptoms which are unfortunately often considered of no significance by both patient and physician. The history which is later so typical may at first be very indefinite, suggesting perhaps the most transient type of indigestion; there may yet be little or no loss of weight and no anemia; there may still be free hydrochloric acid in the stomach not far below the normal amount; and finally, the x-ray may be only faintly suggestive of an organic lesion or may definitely suggest a benign ulcer. It is this early stage of cancer of the stomach which at once offers the most perplexing problems in diagnosis, and the greatest hope for cure with surgical removal.

Since there is no revealed method of prophylaxis against cancer of the stomach, the three considerations of practical interest at present are (1) whether once the disease has begun its course, removal at any stage, even the incipient one, is worthwhile; and (2) with the assumption that removal of the early lesion increases life expectancy and the comfort of the patient, what measures can be taken to increase the percentage of early diagnosis; and (3) what surgical measures can be used to insure the longest period of freedom from recurrence.

The medical profession as well as the laity are frequently impressed and also depressed by the apparent hopelessness of the situation with regard to cancer of the stomach when it attacks their own patients or their own friends. The difficulties in evaluating symptoms and differentiating the insignificant and the ominous ones are discussed and the conclusion not infrequently reached, perhaps with consolatory or condonative implication, that even if an early diagnosis had been made, in such a rapidly metastatic disease not much is gained by removal of the lesion itself.

A recent study of 168 cases of cancer of the stomach in our Clinic was made in an effort to determine the character of the symptoms, their duration, the relation of duration of symptoms to the prognosis, and the effect of early removal upon life expectancy.

These 168 cases of cancer of the stomach were classified as follows into four groups: the first of 56 cases, those whose lesion was of such a character, or whose diagnosis was made early enough, so that the lesion could be removed by partial or total gastrectomy.

The second group of 30 cases, those in whom only palliative changes in the course of the alimentary stream could be made, i.e., by gastrostomy, by gastro-enterostomy, by jejunostomy.

The third group of 32 cases, those in whom only exploration could be done.

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The fourth group of 50 cases, those in whom no operation was considered advisable.

It was felt that these four groups represented roughly four stages in the development of the lesion, graduated from the entirely operable to the entirely inoperable stage, and it was thought that some interesting and possibly some informatory deductions might be made from an analysis and comparison of the following data in these four groups of cases:

(1) The ages of the patients.
(2) The duration of the symptoms.
(3) The chief complaints.
(4) The duration of life after the diagnosis was made.

The general impression that the cancer age is from 40 to 70 years was found to be almost true in this study of cancer of the stomach, since the greatest incidence (54%) was found in the ages of 40 to 59 years, and 35 per cent were between 60 and 70 years. However, it was of interest to note that ten cases or six per cent were between 30 and 39 years, a sufficiently large incidence to make it necessary for the clinician to think of cancer in the patient of the fourth decade who complains of indigestion. Another point of interest in studying the ages of patients in the four groups described above, is that the ratio of patients under 50 years to those over 50 years, is as ½ to 1 in the presumably early stage group, that in which the lesion could be removed, while this ratio changes to 1/3 to 1 in Groups II and III where palliative or exploratory operation only could be done, and to 1/5 to 1 in those considered entirely inoperable. In other words, a relatively younger group sought help in a stage where the lesion could be removed. In certain cases, this probably indicates that the greater age was a contraindication to operation, but it probably means, at least to some degree, that the younger person heeds his symptoms at an earlier stage.

The second point of interest in this comparative study, was the importance of duration of symptoms, a subject usually considered vital by all who refuse to be fatalistic in the matter of cancer of the stomach. It is generally assumed that the length of the history indicates the progress of the lesion, though consideration of two other factors must not be neglected: first, the varying degree of sensitivity to discomfort found in different individuals, and this is usually associated with accuracy of memory of such discomfort, and therefore leads to different degrees of veracity in the relating of the history; secondly, the varying degree of malignancy in the lesion and the reaction of the individual to it. However, in spite of these uncontrollable variants, the length of the period of time between the moment when the patient is first conscious of something wrong and the moment when the diagnosis of cancer of the stomach is made, is a matter of serious consideration.

A study of this phase of the subject in these four groups of cases of carcinoma of the stomach resulted in the following data: In the 53 cases of presumably earlier stage lesions, 32 or 60 per cent had a history of six months or less, while 21 or 35 per cent had a history of over six months. However, in the next two groups representing those with palliative or exploratory operations, and therefore presumably later stage lesions, 61 per cent had a history of six months or less. The totally inoperable cases, however, did show a fewer number of cases with short histories (six months or less), namely, 51 per cent.

The very short history of two months or three months, however, which might by the casual observer be thought to indicate an early stage, was found equally as often in the presumably late stage group as in the presumably early stage group. It seems fair to conclude from this phase of the study that, although the length of history has some prognostic significance, this is less important than would seem logical, a fact which is possibly due to the uncontrollable variants previously mentioned.

The third point of interest was the character of the chief complaints. There are two facts about cancer of the stomach which are also facts about almost any other gastro-intestinal disease: the first, that it may come to the attention of the patient only by general symptoms which point toward trouble in the alimentary tube; but give no clue as to the exact location of this trouble, e.g., abdominal distention; the second, that directly misleading symptoms may occur which, unless followed by careful study, lead to an erroneous diagnosis, e.g., constipation or diarrhoea. It was felt that by a study of the complaints in the various groups of cases, a differentiation might be made of those found in early lesions and those in later lesions. While such was not the case, it was found that the classical symptoms of alarming import, namely, loss of weight and strength and anorexia, were found in increasingly greater incidence with the progress of the lesion, more than twice as frequently in the totally inoperable stage as in the totally operable stage. Furthermore (and this seemed a fact of considerable importance), the symptom of epigastric distress, a chief symptom in the entire series of cancer of the stomach in 42 per cent of cases, was found as chief complaint in more than half of the presumably earlier stage cases, in 43 per cent of those with palliative and exploratory operation, and in only 30 per cent of those considered inoperable. The disquieting fact about these data is that this symptom which in more than half of the cases of cancer of the stomach which were still amenable to treatment, was the chief complaint, is likewise so often the chief complaint in ulcer or gall bladder disease, or a functional disturbance often classified as gastric neurosis, and may often be explained by these relatively innocuous

diagnoses and the actual malignant cause ignored. Another symptom frequently given only casual attention by the physician, namely gaseous eructations, was the complaint for which eight of the 160 cases sought help, and three of these eight were in the group with late lesions. Vomiting was found more frequently in the cases that had palliative or exploratory operations, than in the earlier or later groups. Distinctly misleading symptoms, constipation, diarrhoea, and melena were the chief complaints in 12 cases of this series, five of which were in the early group, and seven in the later groups.

The data on the finding of a palpable mass indicated, as was expected, that prognosis as to operability was poorer in the presence of a palpable mass than when there was none. A palpable mass was found in 31 per cent of the early lesions, as compared with 54 per cent of the later ones. A slightly larger number of early cases, as compared with later ones, had free hydrochloric acid in the gastric contents.

A brief summary of these data concerning the symptomatology of cancer of the stomach in these four groups of cases leads to the conclusion that the character of the symptoms may be heterogeneous, that the textbook syndrome of loss of appetite, weight and strength, is more commonly found in late lesions than in early ones, and that symptoms characteristic of many other gastro-intestinal lesions and distinctly misleading symptoms may characterize the early lesions.

The fourth point of interest in the comparison of data in these four groups of cases was the question of duration of life after the diagnosis was made. Here the question of the value of early diagnosis must find its answer, which in our opinion was an encouraging one. An attempt to conquer in the struggle against the force of the lesion itself and its potential metastases by a removal of the lesion, presupposes an agreement as to the value of any prolongation of life beyond a time when it would otherwise have been ended by disease. Such an agreement is surely uncontested by therapeutists. The data showed that of 86 cases operated upon and followed, 22 of 53 of the first or presumably early group in whom complete removal of the lesion could be done, lived more than a year. In striking contrast is the fact that of 33 cases that had palliative operation, only three lived a year. Furthermore, the survival after partial or complete gastrectomy of one case for nine years, of two cases for six years, of one for five years, of two for four years, of one for three years, and two for two years, all microscopically proved, offers sufficient encouragement to the surgeon and internist to continue the search for early cancer of the stomach and the complete removal of the lesion.

These conclusions lead to a discussion of the second and third considerations of practical interest which were defined as the purpose of this paper; namely, what measures can be taken to increase the percentage of early diagnosis and what surgical measures can be used to insure the longest period of freedom from recurrence.

It is probably true that if all the diagnostic measures which we possess were intelligently used in all cases of cancer of the stomach in the incipient stage, practically none would escape detection. But even those patients who come to the physician with this disease in its early stages may easily be confused with those patients who have an insignificant or a transitory benign lesion. How often does a physician hesitate to urge a complete gastro-intestinal study involving expenditure of time and money, in the case, for example, of a man of 39, presumably not yet in the "cancer age" with a single complaint of gaseous eructations or epigastric distress of only a few weeks' duration, when his symptoms may easily be explained by worry over the stock market, and be cured by dietary care and alkalies. Yet if the duration of life in cancer patients is to be prolonged by early surgery, exhaustive and intelligently executed studies of the alimentary tract must be urged in all patients with gastro-intestinal complaints. The interpretation of the results of these studies must be conservative and careful so that unnecessary surgery will not be done. It is important, for instance, to distinguish in the x-ray findings between an actual lesion and spasm. Prepyloric spasm, prepyloric constriction due to adhesions, and prepyloric constriction due to carcinoma, are easily distinguished on actual visualization and palpation of the stomach, but by fluoroscopic and film methods this is often difficult and only possible in certain cases when measures, either drugs or medical treatment, are used to combat the spasm. It may be of interest here to discuss briefly the differentiating points of diagnosis of cancer and ulcer of the stomach. The day has passed when all lesions of the stomach must be operated upon because they occur in a fertile field for cancer. Large and small ulcers of the stomach have been seen to heal under fluoroscopic vision, and this healing has been checked by *actual* vision and palpation. However, the fact that lesions of the stomach may be differentiated into the benign and the malignant group, puts great responsibility upon the shoulders of the diagnostician. This responsibility can best be met, in our opinion, by a definite policy upon which dependence can be placed in doubtful cases. The policy of our Clinic in such doubtful cases is to decide preoperatively whether there is sufficient reasonable evidence for malignancy to make complete surgical removal of the lesion necessary. Preoperative decisions have been accepted as superior to decisions made during surgical exploration, because the latter have been proved by our experience to be less satisfactory than the former. The early carcinoma may feel and look like an ulcer, and more frequently the calloused

ulcer may look and feel like a carcinoma even to the experienced eye and finger. (Illustrations I and II.) But if preoperative medical management of a doubtful lesion reveals a persistence of occult blood in the stools, a persistence of symptoms in spite of adequate treatment, and a persistence of the x-ray deformity, our experience shows that however innocuous the lesion may appear to the eye and finger, it is malignant, or an unhealable ulcer, and should be radically removed. And if by the same preoperative medical management there is a complete disappearance of occult blood and of symptoms and of x-ray defect, our experience has showed that the lesion is a healable ulcer. The location of the defect is of some value in differential diagnosis: the protruding niche of the lesser curvature media is rarely malignant, whether its size be large or small; whereas the rare greater curvature lesion located exactly on the greater curvature, is probably never benign. The nearer the lesion is to the pyloric sphincter, the greater is the likelihood of malignancy, though there are prepyloric lesions which are healable ulcers. The presence of achlorhydria is a distinct addition to the evidence for malignancy, but the presence of acid does not prove benignity.

ILLUSTRATION I. This is the inside of a stomach removed by partial gastrectomy showing a large benign gastric ulcer. Compare with Illustration II, carcinoma of the stomach.

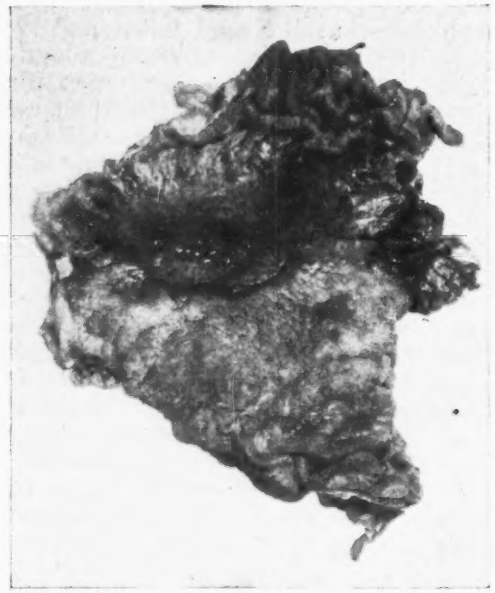

ILLUSTRATION II. This is the inside of a stomach removed by partial gastrectomy showing a lesion which to the eye appears almost identical to the lesion seen in Illustration I. A microscopic examination, however, proved to be carcinoma simplex. These two lesions are shown to demonstrate that, exclusive of those cases of frank gastric cancer which can usually be diagnosed without exploration, surgical exploration to demonstrate possible malignancy in borderline lesions is not of value.

In the frank cases of malignant lesions where there can be no doubt as to the nature of the lesion, the question often arises as to whether it is worth while to explore with the hope of removal of the lesion. In such cases, it is our opinion that radical surgery offers the best chance for extension of life, even in those cases where there is some evidence of metastases.

The third point which we have defined for discussion in this paper now arises; namely, the surgical measures which can be used to insure the longest possible freedom from recurrence.

In discussing the surgical treatment of cancer of the stomach, one must admit that not infrequently, because of factors already mentioned, surgery upon the stomach for malignancy must often be done when conditions are quite unsatisfactory. The ideal surgical situation in relation to cancer of the stomach is a small lesion of early malignancy located near the pylorus, permitting thus extensive and easy partial gastrectomy. Unfortunately, this early discovery is often not possible and surgery must frequently be applied to gastric malignancy under much less favorable conditions.

There are certain factors which have to do with the success of surgery in dealing with malignancy of the stomach, one of the most important of which is anesthesia. We have, in our experience with gastric resection, passed through several stages as relates to the type of anesthesia, beginning with ether, then with local anesthesia, next with spinal anesthesia, and now combined avertin, intratracheal ethylene and regional anesthesia. This latter combination of anesthetics has proved most satisfactory in our hands.

The disadvantage of ether anesthesia for gastric resections is that it tends to produce shock, particularly when patients have to be carried to considerable depth and kept under it for a comparatively long period of time as is necessary in gastric resections.

The difficulty of nitrous oxide and ethylene anesthesia is that they often do not produce ade-

quate relaxation of the abdominal wall so that high anastomoses can with ease and safety be made to short gastric stumps after extensive partial gastrectomy. This is in a considerable measure true even when regional anesthesia is added to either nitrous oxide or ethylene anesthesia.

When spinal anesthesia became popular, as it did a few years ago, it seemed possible that it might well supply ideal operating conditions for gastric resection, particularly in those patients who often fall into the bad risk group. In a considerable experience with this type of anesthesia in operating upon patients who require extensive, lengthy operative procedures, spinal anesthesia has proved disappointing and even dangerous. The disadvantages of spinal anesthesia in patients with upper abdominal lesions requiring prolonged operations are two; one, that a large dose of the drug must be employed in order to prolong the anesthesia as much as possible; two, the anesthesia must be carried fairly high in order to produce loss of sensation well above the operative level. Both of these factors tend to produce marked drops in blood pressure and so increase the danger of the procedure. Another unfavorable factor in the employment of spinal anesthesia in gastric resections is the fact that one cannot be sure how long the anesthesia lasts. Even with large doses of novocain, anesthesia may fail at the end of an hour. After an hour the duration of the anesthesia is always very uncertain. When anesthesia fails in this situation, a general anesthetic must then be given to complete the procedure and to close the abdominal wall. This involves often ether, nitrous oxide or ethylene given so that the patient is carried to considerable depths of anesthesia. At this time, the patient has already been submitted to a quite shocking procedure and the addition of a general anesthetic of sufficient depth to permit the completion of a high anastomosis or closure of the abdominal wall often results in very definite degrees of shock, and so provides features calculated to increase the mortality in these cases.

Since our anesthetists, Dr. L. F. Sise and Dr. P. D. Woodbridge have made use of the present plan of combined avertin, intratracheal ethylene and regional anesthesia, anesthesia conditions for these radical gastric resections have been very much improved.*

The present plan, therefore, is the employment of sixty to ninety milligrams of avertin per kilo of body weight given to the patient while still in her room. On the operating table, patients are placed under ethylene and when well under ethylene by means of the laryngoscope, the intratracheal catheter containing the Waters' Balloon is passed between the vocal cords into the trachea. The balloon on the end of the catheter is then blown up so that there is a tight fit about the tube in the trachea and the intratracheal catheter is connected with the ethylene apparatus which has attached to it a carbon dioxide extractor. This carbon dioxide extractor, which is similar to that on a basal metabolism apparatus, has also proved of great value in that it keeps the heat and moisture within the closed circuit, it extracts carbon dioxide so that it is not being returned to the patient to produce the stertorous type of respiration, and, in addition, markedly diminishes the amount of ethylene and nitrous oxide which must be employed.

The operability in carcinoma of the stomach is particularly influenced by the location of the lesion, granted, of course, that there are not prohibiting metastases in the gastro-hepatic lymph glands and in the liver. As already stated, the most operable type of carcinoma is that arising in the prepyloric region without extension, allowing thus a large portion of normal stomach to be resected with a margin of safety beyond the lesion. The most unfavorable site for gastric carcinoma is that occurring along the lesser curvature, because malignant lesions here tend to contract and pull the esophageal opening into the stomach closer to the pylorus, so that there is a limited margin of normal stomach wall on the lesser curvature between the lesion itself and the point where the esophagus enters the stomach. Several times we have demonstrated a malignant lesion on the lesser curvature of the stomach which was operable so far as removability of the lesion, together with the absence of metastases, was concerned, but because of the fact that the lesion had so extended along the lesser curvature as to involve or almost involve the esophageal opening into the stomach, a sufficient gastric remnant could not be left so that a satisfactory anastomosis could be done. In such cases we have twice excised a portion of the esophagus as it enters the stomach, but this makes anastomosis between the jejunum and irregular gastric stump, a part of which is the esophagus, difficult and dangerous from the point of view of leakage.

The mobilization of the left lobe of the liver by incision of its ligamentous attachment to the diaphragm, an avascular structure, makes technical approach to the cardiac end of the stomach very much more easy and in cases with lesser curvature extension, it has twice proved possible for us to do successfully a complete and total gastrectomy with anastomosis of the jejunum to the esophageal opening into the stomach.

Dr. H. M. Clute of this Clinic published such a successful case in 1930, a patient with extensive carcinoma of the entire stomach but without metastases. In this case he was able to remove the entire stomach and to anastomose the jejunum to the esophagus. This patient lived

*Woodbridge, P. D.: Better Gas Anesthesia. The carbon dioxide absorption method. New Eng. J. Med. 208:632 (Mar. 23) 1933.

in comfort and was able to support herself over a period of three and a half years.

Total removal of the stomach with anastomosis of the jejunum to the esophagus has recently again been successfully accomplished by one of us (F. H. L.) in a patient with the leather bottle type of carcinoma of the stomach without lymphatic or liver metastases. (Illustration III.)

ILLUSTRATION III. An x-ray picture following the ingestion of bismuth in a patient on whom a total gastrectomy was successfully done, the jejunum being anastomosed to the esophagus. This x-ray was taken ten and a half weeks after operation.

Note the passage of food at the arrow directly from the esophagus into the small intestine.

The mortality of total gastrectomy will of necessity always be high, but based upon our experience now with four cases, two of which have been successful, it seems a justifiable risk to take if there are no evidences of metastases outside of the stomach itself, even though the lesion be an extensive one.

Other than from the point of view of technical features, there is little to be said concerning the operation of gastric resection except as relates to the decision for or against it in cases with extensive carcinoma and with metastases. One must in these cases make up his mind as to whether a palliative gastro-enterostomy or a gastric resection should be done. As the result of our experience with this situation, we feel very strongly that if the patient is not too bad a risk, partial gastrectomy with the removal of the extensive lesion, even in the presence of liver metastases or gland metastases, is a much superior operation to gastro-enterostomy, and that it will provide the patient with greater comfort and prolong his life to a greater extent than will palliative gastro-enterostomy. Palliative gastro-enterostomy, in our hands, has sometimes prolonged life, but frequently has not made the patient much more comfortable.

Another surgical problem which is frequently difficult to settle in very extensive carcinoma of the stomach is whether one is justified in doing jejunostomy in the hopeless cases. This is a problem which we have all at times found difficult to settle. Is it better to permit patients with carcinoma of the stomach, who are utterly incurable but who are unable to take fluids and food, to go on and die, or should they be made more comfortable and their life prolonged by the institution of jejunostomy? No acceptable position can be taken on this situation. It often is a decision which must be made by the family after they have been made familiar with all of the circumstances and sometimes by the patient himself.

A discussion of the technical features of partial gastrectomy should, in our opinion, be reserved largely for a surgical journal which is read by those who are interested primarily in surgery. There are, however, a few technical features, and one perhaps original suggestion based upon our operative experience with a considerable number of these operations that may be worth speaking of in connection with this operation.

Gastric resection for cancer usually must be of such extensiveness that any consideration of re-anastomosis between the cut end of the stomach and the duodenum is not feasible. Therefore, following partial gastrectomy for cancer, the problem is practically always that of re-establishment of the alimentary stream by anastomosis of the jejunum to the stump of the stomach. This may be accomplished by one of two plans: either the Billroth Number Two operation, or by some modification of the operation which, in this country, is described under the name of the Polya operation. We have always preferred to employ the posterior Polya operation (Ill. IV) because it saves time in that one row of sutures closing the cut end of the stomach is eliminated, and because it has always seemed to us that posterior Polya anastomoses functioned better than anterior anastomoses and were, in addition, more physiologic. When a large portion of the stomach is removed, as in resections for gastric cancer, leaving less than a third or a fourth of the stomach, it is often difficult, as in the Billroth operation, to do an anastomosis of the gastro-enterostomy type between the anterior or posterior wall of the stomach and the jejunum, since the remaining segment of stomach frequently retracts into the left hypochondrium where it is difficult to anastomose the jejunum to it. We have, therefore, made it a rule to employ the posterior Polya type of anastomosis, suturing

the segment of jejunum which is to be anastomosed to the stomach to the posterior wall of the stomach before the lower portion of the stomach and its contained lesion is cut away. This, as has frequently been demonstrated and stated, prevents retraction of the gastric stump and makes suture of the jejunum to the end of the stomach much easier.

We have been particularly interested in a method of dealing with the proximal stump of the jejunum which has proved valuable in our hands, was devised by one of us (F. H. L.), and makes for better postoperative functional results than some of the previously employed procedures.

Following removal of the distal portion of the stomach and anastomosis of the jejunum to the remaining gastric stump, one of two procedures as relates to the proximal jejunum may be employed: a long loop of jejunum may be brought up over the transverse colon and anastomosed to the cut end of the stomach by the plan described and devised by Dr. Donald Balfour, called the anticolic Polya anastomosis, or the transverse colon may be brought out upon the abdominal wall and an incision made in its posterior root through which is passed a loop of jejunum to be anastomosed to the cut end of the stomach. This is the so-called posterior Polya anastomosis.

The point which we wish to suggest in connection with this is shown in Illustration IV. After an opening has been made in the posterior leaf of the transverse mesocolon, the jejunum, where it emerges from its retroperitoneal portion, is put upon the stretch, the ligament of Treitz demonstrated, and the ligament cut by scissors up to its root. The incision of the ligament of Treitz then makes possible the transplantation of the proximal loop of jejunum entirely above the transverse mesocolon so that after the anastomosis is complete, the proximal section of the jejunum which is sutured to the lesser gastric curvature is entirely above the posterior leaf of the transverse mesocolon and but a single loop of bowel, the distal loop of the jejunum which runs from the greater curvature down into the peritoneal cavity, emerges through the rent in the transverse mesocolon. This makes possible the approximation of the rent in the transverse mesocolon about a single loop of bowel (Illustration IV), preventing thus the

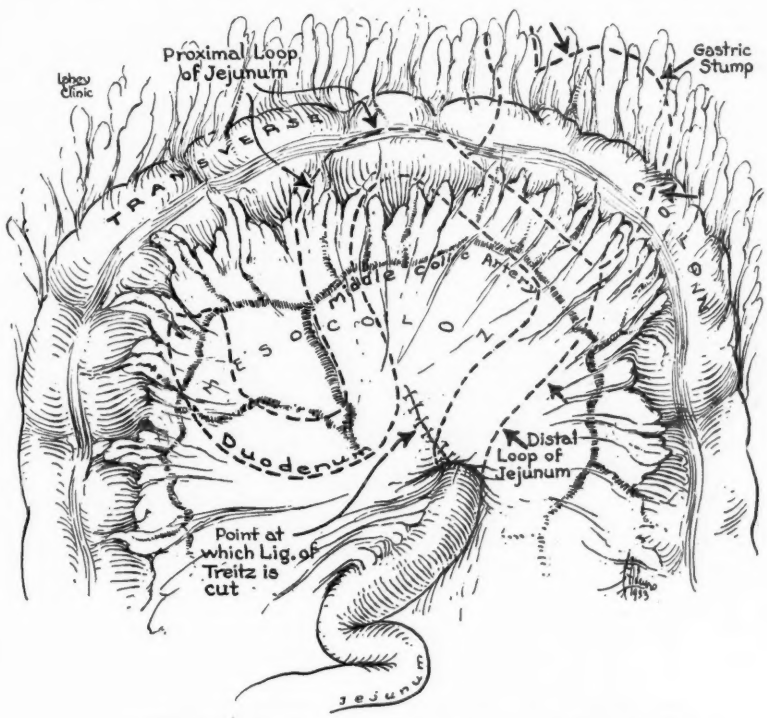

ILLUSTRATION IV. This semi-diagrammatic illustration is shown to demonstrate the plan of transplanting the proximal loop of the jejunum above the mesocolon into what was the lesser peritoneal cavity. The gastric stump and the jejunum anastomosed to it is shown in outline with dashes through the turned up transverse colon and mesocolon. Note that the proximal loop of jejunum runs directly from the duodenum to the stomach and that as the result of incising the ligament of Treitz, it has been transplanted entirely above the mesocolon. Note that the incision of the ligament of Treitz opens the mesocolon and that by this plan of transplanting the proximal loop of jejunum, but a single loop of jejunum, the distal one, emerges through the mesocolon, permitting the mesocolon at the point where the ligament of Treitz was incised (indicated by arrows) to be closed accurately about it.

danger of hernia and making the course of the proximal loop of bowel an unangulated one. This plan of dealing with the proximal jejunal loop in gastric resections has now been utilized in over twenty cases and has proved a very satisfactory one.

There is little further to be said as to the surgery of gastric cancer except that in our opinion it must be aggressive in character. One must exercise the greatest diagnostic caution in making sure that the lesion is not a healable ulcer. Once having settled that the lesion in the stomach is malignant, it is then no time for faint-hearted surgery. The salvation of patients with cancer of the stomach, exclusive of early diagnosis, is in radical and extensive operations even up to total removal of the stomach.

CONCLUSIONS

The salvation of patients with carcinoma of the stomach is in early diagnosis.

Early diagnosis can be made only when x-ray examinations of the stomach are made upon evidence which is only suspicious, and it must be accepted that many will prove negative.

The duration of the history is not a criterion of the extent of the disease.

Partial gastrectomy even in patients with metastases gives better results than palliative gastro-enterostomy.

Complete gastrectomy, even with a high mortality rate, is justifiable in selected cases.

Early diagnosis and radical partial gastrectomy offer definite hope for cure, as demonstrated by our cancer patients alive and well nine years, six years, five years, four years, three years, and two years after operation.

A method of dealing with the proximal loop of the jejunum in posterior Polya resections of the stomach is described and illustrated.

NEW HAMPSHIRE MEDICAL SOCIETY

ACUTE PANCREATITIS—WITH A REVIEW OF FIFTY-FOUR OPERATIVE CASES*

BY P. E. TRUESDALE, M.D.†

SPEAKING before the New York Pathological Society in 1889, Reginald H. Fitz[1] made a notable contribution to the study of acute pancreatitis. At that time the origin of the disease was attributed to the extension of a gastroduodenal inflammation along the pancreatic duct. The theory of chemical and autodigestive changes and the frequent accompaniment of cholelithiasis in cases of acute pancreatitis had been noted by investigators such as Opie[2], Flexner[3], and others. In a case operated upon by Bloodgood[4] a gall stone the size of a pea was found occluding the ampulla of Vater, thus forming a continuous passage through which the bile traveled from the common duct directly into the pancreatic duct. The inference was made that in many cases a stone might become temporarily lodged long enough to allow damage to the pancreas and then escape, leaving no other evidence of its presence. Fitz by a comprehensive study of the terminal changes in the pancreas, outlined a more definite symptomatology and a more precise pathology than had hitherto been known.

Considerable progress in the clinical recognition of acute pancreatitis has been made since this time, but, owing to the relatively infrequent incidence of the disease, opinion has not crystallized on a definite theory as to etiology. The mortality rate remains high. McWhorter[5] considers diagnosis still difficult and regrets the high mortality statistics in this "highly fatal condition". Stetten[6] calls the acute fulminating hemorrhagic type an almost hopeless catastrophe. In a collection of 1,510 cases from German clinics 149, or 10 per cent of the patients died before operative intervention and 68 per cent died following operation. In Stetten's series the mortality was 71 per cent.

Two theories as to etiology are frequently propounded. An influx of bile or duodenal contents through the duct may start the process, or an infection may occur from lymphatic invasion from without, usually from the biliary system. Moscheowitz[7] said that he was not sure that the much lauded operation of cholecystostomy saved more than a small percentage of cases. He did two exploratory laparotomies for acute pancreatitis and merely removed the appendix. Both patients made an uninterrupted recovery, which indicates that perhaps the disease often subsides spontaneously. A third patient was operated upon for acute cholecystitis. No gall stones were found, but there was an acute hemorrhagic pancreatitis. Cholecystostomy was done. The night before the patient was to be discharged from the hospital another attack of acute pancreatitis occurred and the patient died.

The close anatomical relationship of the pancreatic duct and the common bile duct is an important factor, however, in the associated

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pathology. Egdahl[8], in an analysis of 108 cases, says that about 42 per cent of cases of acute pancreatitis are associated with gall stones, and considers them the most common single cause. In our series of 54 cases of acute pancreatitis, gall stones were present in 49 per cent. Speese[9] maintains that retrojection of bile into the ducts of the pancreas is the most likely cause of acute pancreatitis; the presence of bacteria in the bile favors the development of the process. Some authorities, however, believe it more probable that, even in the acute cases, the infection reaches the pancreas by way of the lymphatics. Judd, Mann, and Giordano[10] studied the rôle played by the bile in producing pancreatitis and observed the anatomic relations of the common duct to the duct of Wirsung. In a survey of 200 consecutive autopsies they proved that in only 3.5 per cent of the cases it would be anatomically possible for obstruction at the ampulla of Vater to convert the two ducts into a continuous channel and permit bile to pass into the pancreatic duct. They also found that the muscle of Oddi can contract to convert the two ducts into one in very few cases, and that usually its contraction constricts both ducts.

Mann also investigated the degree of pressure necessary to force bile into the pancreatic duct. In most cases it required 500 millimeters. Bile was injected into the duct but did not produce pancreatitis until the pressure was much greater than that which could be produced by deep respiration or vomiting. Thus these investigations on animals over a long period of time led the authors to conclude that a reflux of bile into the pancreatic duct is rare and that this could not be considered a common cause of acute pancreatitis.

There was only one case in our series of a stone lodging in the ampulla of Vater. The patient was admitted with a history of recurring attacks of pain during an interval of 18 months. These attacks were accompanied by vomiting and slight jaundice. A diagnosis of chronic cholecystitis with cholelithiasis was made. Cholecystectomy with drainage was done and several stones removed from the cystic duct. Seven weeks later the patient returned with severe epigastric pain. She was dyspneic and cyanotic, and died a few hours after admission. No physical diagnosis was made. Postmortem examination revealed an acute hemorrhagic pancreatitis. A very small stone was found lodged in the ampulla of Vater. (Fig. 1.)

There is also evidence that in some cases infection may reach the pancreas through the blood stream, but more frequently it is by way of the lymphatics. During embryonic life the lymphatics of the pancreas bear a close relationship to the lymphatics of the bile-ducts. That portion of the pancreas which is derived from the ventral anlage develops from one of two buds which grow out from the primitive intestine very close to the liver bud or even from the lower part of the liver bud.

To understand the manner of pancreatic infection through the lymphatics, a careful review must be made of the lymph vessels of the pancreas, the various groups of nodes, the portion drained, and their close association with the

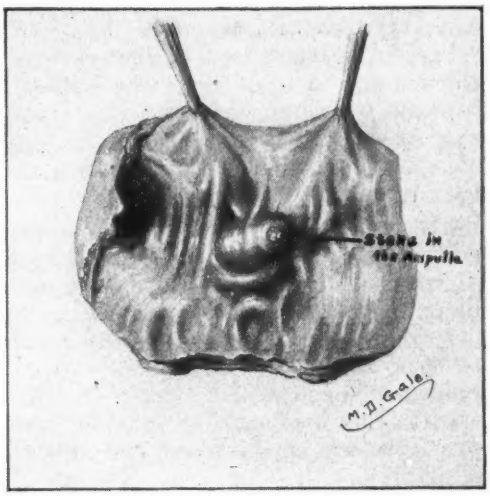

FIG. 1. Inner wall of the duodenum showing a stone in the ampulla occluding the common duct.

lymphatics of the liver and gall bladder. These lymphatics, in turn, are part of the lymph channels accompanying the inferior and superior

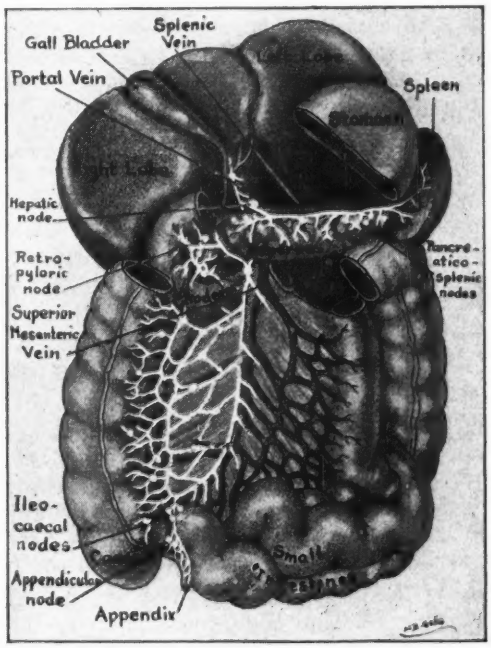

FIG. 2. Lymphatic distribution from the appendix and the ascending colon to the pancreas.

mesenteric veins which drain the entire colon. Thus, bacillus-laden lymph from as remote a focus of infection as an appendiceal abscess might readily reach the pancreas. (Fig. 2.)

In 1911 Franke[11] demonstrated the anas-

tomoses of the lymphatics of the gall bladder with those of the head of the pancreas. He showed that areas of inflammation in the pancreas correspond with the lymphatic distribution. A node at the neck of the gall bladder ordinarily called the sentinel gland, communicates with the lymph vessels of the pancreas. This node is frequently enlarged in cases of chronic pancreatitis. There is also close connection between the afferent and efferent branches of the lymphatics of the pancreas and the duodenum. A blocking of the nodes in any part of the lymphatic system makes possible a reversal of the flow of lymph into efferent pancreatic vessels and in this way infection is readily carried to the pancreas.

The lymphatic vessels of the pancreas arise from a network about the pancreatic lobules. These trunks anastomose freely on the surface of the pancreas. Some terminate in the splenic glands which send vessels to the celiac glands. Others pass directly to the celiac glands. The lymphatics at the head of the pancreas communicate with the duodenal lymphatics and the lymphatic vessels of the lower end of the common duct.

Deaver[12] concluded that in many cases of acute pancreatitis the infection was borne by the lymphatics because the disease is not often associated with the lodgment of a gall stone in the ampulla of Vater. Besides, in a fair percentage of cases gall stones are not present. In cases with complications the focus of infection might be exceedingly difficult to determine. The views presented show the wide lack of agreement among authorities.

SYMPTOMS

The symptoms of acute pancreatitis are striking and quite typical of the infection. The organ, however, is deeply situated in the body and does not give surface manifestations until markedly affected. There are so many other lesions in the upper abdomen which cause severe pain that the pancreas may not be considered in making the diagnosis.

The onset is usually sudden. Severe agonizing pain is referred to the epigastrium, radiating to the sides and back. Moynihan[13] describes the pain as the most severe type encountered from any lesion within the abdomen. He believes that no other catastrophe within the peritoneal cavity can produce so profound a collapse.

Pressure of the engorged pancreas on the duodenum causes vomiting. There may be slight jaundice and clay-colored stools. In the more fulminating cases there is severe prostration sometimes followed quickly by death. To describe this condition the term "pancreatic apoplexy" is used.

It is well to keep in mind the fact that acute pancreatitis is a disease of marked variation in the degree of its severity from a mild inflammatory process which subsides spontaneously to the fulminating hemorrhagic type which causes death soon after the onset of the attack. This severe type is a well-recognized cause of sudden death, but such cases are seldom recognized except at autopsy. For example, Graham[14] has recorded a case with a history of repeated attacks of pain over an interval of six months. A diagnosis of appendicitis was made and the appendix removed. The attacks of pain recurred. At a second operation an acute hemorrhagic pancreatitis was found. The patient made a complete recovery and was entirely relieved.

Butler and Delprat[15] think that small hemorrhages occur frequently in the pancreas and cause gastric upsets which have been attributed to indiscretions in diet. If the hemorrhage occurs in the head of the pancreas and if pathological changes exist in the bile passages, a pancreatitis often results. On the other hand, if the hemorrhage is slight and arises in the body or tail of the pancreas, recovery is to be expected without marked alteration or destruction of the gland.

As an example of the more severe hemorrhagic type, U.W., suffering from severe abdominal pain accompanied by vomiting, entered our hospital September 4, 1925 several days after the onset of the attack. Two years previously his appendix was removed after it had perforated. On that occasion examination of the gallbladder revealed the presence of gall stones. Before leaving the hospital the patient was informed of the condition of cholelithiasis and advised to return for operation if symptoms warranted. In spite of this admonition, when the attacks of abdominal pain occurred the patient delayed five days before reëntering the hospital. Cholecystectomy was done and several strips of rubber dam were used for drains. The pancreas was felt to be enlarged but there was no evidence of fat necrosis. The patient grew rapidly worse and died five days after operation. Autopsy revealed an acute hemorrhagic pancreatitis with areas of fat necrosis showing only on the under side of the mesocolon.

The lesson to be derived from this experience leads one to realize that the discovery of an acutely inflamed gallbladder filled with stones may not be the main pathological process causing an acute attack, the result of which may prove fatal. It is incumbent upon the surgeon to exclude acute pancreatitis both by manual and visual examination of this organ and by a careful search for fat necrosis.

REVIEW OF CASES

There were 54 operative cases of acute pancreatitis in our clinic, 42 in females, 12 in males. Twelve of the 54 cases were of the acute hemorrhagic type. Eleven out of the 54 patients

died, a mortality of 20.5 per cent. The primary cause of death was respectively diabetic coma, acute nephritis, valvular heart disease, cirrhosis of the liver, ruptured gallbladder (two cases), acute cholecystitis, and thrombophlebitis of the splenic vein. In two cases the pancreas had sloughed and there was free blood in the peritoneal cavity. In nine of the cases there was considerable fatty metamorphosis of the liver and many areas of fat necrosis on the pancreas, omentum, mesocolon, pylorus, and intestines.

Seven of the eleven fatal cases were of the fulminating hemorrhagic type. In eight of these the condition was discovered at autopsy.

The diagnosis of acute pancreatitis was made after exploratory laparotomy in 28 of the cases. In 18 a correct diagnosis was made prior to operation. A palpable mass in the epigastrium enlarged and tender sometimes aided in the differentiation. Since most of the cases were associated with acute cholecystitis, it was difficult to interpret symptoms correctly, especially since they might be referable to gallbladder disease.

In 47 or 89 per cent of the 54 cases cholecystitis was present. Gall stones were found in 26 cases. In one a gall stone had lodged in the ampulla of Vater. Seven cases were complicated by appendicitis. In two, large calcified lymph glands were seen in the region of the head of the pancreas. In six there was marked sloughing of the pancreas. Two of these cases were fatal.

One case was traumatic, the attack occurring after a fall from a ladder; at least the onset of the disease was thus accounted for in the records, but it is possible that the acute attack may have caused the fall from the ladder. There were multiple contusions of the abdomen and hemorrhage into the pancreas. The following day a hard mass was felt in the head of the pancreas. After drainage of the pancreas the man recovered.

In 17 cases the pancreas was incised or penetrated with the finger and drained. In one case the tail was involved, in three the head and tail, and in seven the entire organ.

In eight instances, portions of the pancreatic tissue were excised for microscopic examination. Biopsy of the pancreas may result in hemorrhage sometimes very difficult to control.

Operative treatment as follows:

Cholecystectomy and drainage	6 cases
Drainage of biliary passages	21 cases
Drainage of pancreas only	4 cases
Combined drainage of pancreas and bile ducts	13 cases
Total	44 cases
Discovered at autopsy	10 cases

In the majority of the cases the acute disturbance in the pancreas cleared up when the bile passages were drained. Surgical interference was prompt and at operation the presence of areas of fat necrosis on the peritoneum confirmed the preoperative diagnosis. In the hemorrhagic cases there was bloody fluid in the abdomen and necrosis of pancreatic tissue.

The phenomenon of hemorrhage in the fulminating cases is still unsolved, but is thought to be due to the activation of the pancreatic secretion trypsinogen. When infection causes cellular death, the trypsinogen is transformed into trypsin which brings about autolysis of the pancreas. All the conditions which may cause this activation of pancreatic juice are not known.

In the acute cases without hemorrhage, the presence of fat necrosis is considered the pathognomonic sign. Langerhans first demonstrated fat necrosis by the action of fresh pancreatic juice upon living fat tissue. This lesion results from the escape of pancreatic ferments into fat tissue, splitting the fats into fatty acid and glycerine. The presence of fat necrosis was formerly interpreted as a fatal sign, but we know today that, although the changes in the gland are rapid and destructive, prompt surgical interference assures recovery in the majority of cases.

We are indebted to the late Dr. C. A. Porter[16] of Boston for suggesting a radical measure in dealing surgically with acute hemorrhagic pancreatitis. It consisted in making an incision over the entire length of the pancreas. He described this method in an article which appeared in the *Boston Medical and Surgical Journal* in 1903 shortly before I had operated upon my first case. I adopted the method and believed that in so doing I saved the patient.

SUMMARY

Acute pancreatitis is an acute infection in a deep-seated vital organ, often fulminating, occasionally destructive. No other abdominal ailment has initial symptoms more characteristic. It is manifested by the acute severity of onset, agonizing epigastric pain accompanied by vomiting. The acute fulminating cases demand immediate intervention. Cases of moderate severity may yield to drainage of the bile passages. When the hemorrhage is diffuse and involves the entire organ, the pancreas should be opened longitudinally and drained liberally, care being taken not to incur the liability of massive hemorrhage. The recognition of fat necrosis is often the key to the diagnosis.

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DISCUSSION

DR. HERBERT L. TAYLOR, Portsmouth: The possibility of acute pancreatitis, if borne in mind whenever an acute abdominal mishap presents itself, offers no greater difficulty in diagnosis than does any other acute surgical condition. Acute pancreatitis is not a primary disease but rather a sequela. One must face the fact that biliary disease is usually the precursor. Previous gastro-intestinal disorders are of great significance. The symptoms are due to local pancreatic irritation, as well as those due to the circulation of toxic products. Inflammation of the pancreas results in edema and swelling of that organ. Stretching of the pancreatic capsule induces pain. Diaphragmatic excursion may be obstructed and biliary drainage impeded. Pressure on the semilunar ganglion should be taken into consideration in explaining the symptomatology. Circulation of foreign protein and its products of incomplete digestion may, in part, explain the severe toxemia present. Digestion of blood vessels contributes the hemorrhagic features of the picture in this disease.

Inflammation of the peritoneum is due to the irritants circulating under the serosa. Constant epigastric pain is most frequently encountered. It is splitting in character as though something within were trying to force its way out. Some patients have general abdominal pain, and others have right or left hypochondriac pain or back ache.

The pain in acute pancreatitis is of intense severity, and morphine frequently repeated often fails to relieve it.

Vomiting is also a very troublesome and persistent symptom. Emesis is never fecal in character. Gastric lavage relieves it. The foreign protein present in the circulation calls forth a peculiar train of symptoms, such as shock, collapse, cyanosis, dyspnea and skin reactions. Elevation of temperature does not help, because it usually varies a great deal. The pulse rises out of all proportion to the temperature ratio. Icterus due to pressure on the bile duct is never severe. Epigastric tenderness is frequently present. Constipation and not diarrhea is the rule. The silent belly offers a contrast to the active one of mechanical obstruction.

In animals, in the absence of an obstruction at the ampulla of Vater, we have been unable to produce regurgitation into the duct. In man, a reflux of bile into the pancreatic duct through the agency of a stone impacted in the ampulla has frequently given rise to acute pancreatitis, but the mechanism accounts for only a minority of instances. Anatomic possibilities are retained, and possibly such reflux of bile may be conditional through disturbance in the sphincter, regulating the mechanism of the ampulla. The actual occurrence of pancreatic necrosis through such an agency in man remains to be demonstrated.

Following acute infections in the biliary tract, cloudy swelling of the pancreas is regularly observed and actual necrosis does not result.

Clinically, pancreatic injury of a similar character appears to be an occasional accompaniment of acute infection of the gallbladder. Proof that these pancreatic changes are precursors of and eventuate in an actual necrosis is lacking, but that in the presence of an activating influence for trypsinogen such changes may eventuate in actual necrosis, it appears to be substantiated. The effective activation of trypsinogen would appear to be the essential factor. Although pancreatic tissue and the products of its disintegration may activate trypsinogen in vitro, animal experimentation demonstrates that injury to the gland is affected through ligation of the duct. Infection or mechanical trauma is usually inadequate as a single factor to produce acute necrosis.

The results indicate the direction of subsequent investigation, namely, that the solution of the cause of, probably, many instances of acute necrosis is to be found in a combination of factors which alone are inadequate.

Now, as a matter of fact, few operations have been done within a few hours of the onset of the disease. Usually the patient does not come under surgical care until the second or third day of the disease, and, in many of these cases, as in other cases of diffuse peritonitis, it is safer sometimes to encourage localization of the process before instituting drainage. Certainly, one should not wait until the patient is moribund from sepsis. Sometimes it is possible to wait until well-localized tumefaction indicates the presence of an abscess or of gangrene, but, whenever a case is seen before symptoms of profuse peritonitis arise, the surgeon should lose no time in opening the abdomen to evacuate the toxic extravasation.

As to the matter of treatment, the important point is to save life. One must relieve the pressure of the semilunar ganglion and common duct by opening the pancreatic capsule. If the patient's condition is good, the operation of choice is cholecystectomy in order to remove the source of infection. At other times, the drainage of the gallbladder is all the patient will stand, and therefore it must suffice to drain the pancreas. Proper and early treatment of biliary disease will decrease the mortality rate of acute pancreatitis. The time to operate is when the disease is still confined to the gallbladder.

The pancreas is surrounded in man by abdominal vessels of importance. The pancreatic fluid in the peritoneal cavity causes fat necrosis and fatal peritonitis. One may expose the pancreas through the gastric hepatic ligament or through the gastrocolic ligament. One can obtain the best view of the organ through the latter method.

Operations for pancreatitis vary according to the stage of the disease. In acute conditions where the pancreas is greatly swollen, short incisions are made into the pancreas to relieve tension, and are enlarged by inserting closed forceps and spreading the jaws. Drainage with tubes and gauze is carried down to the wound in the pancreas. If there is free oozing, the supply of gauze drainage should be abundant. The approach to the pancreas is usually made through the gastrocolic omentum. The necessity for incision into the pancreas must be decided by the character of the inflammation. The subacute and chronic cases require only drainage of gallbladder or common duct.

Pancreatic disease is to be suspected if, as soon as the abdomen is opened, there is a bloody exudate,

or if there is a fat necrosis. Then, too, marked distention of the transverse colon, without obstruction, is a valuable sign. The stomach may be displaced in various directions by the swollen gland. The pancreas should be approached at the point of bulging.

There is no object in incising the pancreas unless it appears distended, or unless there is a hematoma present. There is less danger of absorption from the serous surface of the peritoneum than from the retroperitoneal cellular tissues. The pancreas should be opened only after carefully protecting the general peritoneal cavity by a coffer dam of gauze, and a local collection of fluid may be evacuated by an aspirator. Also, the hematoma, or abscessed cavity, should be incised only after its contents have been withdrawn. The biliary tract should not be interfered with, except for very positive indications, and only when the patient is in reasonably good condition.

DR. W. J. PAUL DYE, Wolfeboro: I would like to know a bit more about the actual surgical technique used in the approach to the pancreas, the character and indications for placing drains and the type of drains used in such procedure.

DR. RICHARD W. ROBINSON, Laconia: I would like to ask Dr. Truesdale if there is still considered to be any relationship between mumps and acute pancreatitis, and also while it has been said that the condition is readily diagnosed if it is thought about just what the distinguishing signs are between an acute abdomen, due to hemorrhagic pancreatitis and such a condition as perforating gastric ulcer without previous gastric symptoms.

DR. PHILEMON E. TRUESDALE: I was glad to hear Dr. Taylor speak about the inflammatory process outside the peritoneum. By that, I assume, he meant the infection. That is peritonitis, not actually an inflammatory process in the serosa itself, but an infection that travels through the lymphatics under the peritoneum. The relationship between mumps and acute pancreatitis I do not know. We do know that parotitis is a not infrequent complication of other remote infections.

Dr. Dye spoke about the technique of the operation. Ordinarily, when you are not sure of the diagnosis, you would open the abdomen by a vertical paramedial incision. It is the most satisfactory approach. However, if one knew definitely that he was doing an operation for acute hemorrhagic pancreatitis, he should make a transverse incision. That would make the entire length of the pancreas accessible. For drains, we use rubber dam. We feel that it is advisable to make a long opening in the pancreas. If nothing more is done than a decompression and drainage, this may control the disease. The incision through the anterior surface of the pancreas should extend thoughout the length of this organ. This operation was originally advocated by Dr. C. A. Porter, as I have mentioned in the text.

In the other group of cases where radical measures are not necessary and where the disease can be treated by an operation that deals with some other structure than the pancreas, such as the gallbladder or the common duct, I think one of the other speakers mentioned cholecystectomy as removing the focus of infection. It does, and so far as that goes, it is very helpful. But you have to do something more than remove the focus of infection, if such it is, because the inflammatory process in the head of the pancreas leaves all the tissue engorged and under tension. Usually there is some interference with the flow of bile out to the duodenum. If that bile is sidetracked, you have gained so much more in relieving the stress that is being placed upon the pancreas. So cholecystectomy, if done, should be supplemented by drainage of the common duct.

I would say that in the acute hemorrhagic type, a radical opening in the pancreas would be an effective procedure, providing the surgeon is careful not to produce alarming hemorrhage.

In the other class, drainage of the gallbladder, or the removal of the gall bladder and drainage of the common duct, would be the procedure. In order to dislodge small stones impacted at the ampulla, Dr. F. H. Lahey uses suction, while Dr. David Cheever advocated putting a catheter into the common duct and washing it out. Either method will clear the common duct and establish effective drainage into the duodenum after the pancreatitis subsides.

Dr. Robinson asked for a discussion of the differential diagnosis. The history, I should say, is the most important element in the differential diagnosis. The onset of acute hemorrhagic pancreatitis is usually sudden, the pain excruciating, and accompanied by nausea and vomiting. The laboratory tests, the x-ray, the white count, the blood sugar, all help, but the history and the physical examination are all important. We find that many of the patients with acute pancreatitis have normal urine and practically a normal blood sugar. Dr. Robinson spoke about differentiating acute pancreatitis and perforated gastric ulcer. If the patient has a history of ulcer before the attack, that would make one suspect perforation of an ulcer. In perforated ulcer, however, there is one sign that is unmistakable, and you can bank on it in over ninety per cent of the cases. That is the board-like rigidity of the whole abdominal wall. If that sign is discovered on palpation, you may say with a fair degree of certainty that the patient has a perforated peptic ulcer. On the other hand, in pancreatitis, the rigidity of the muscles will be limited to the upper abdomen.

About two months ago, there was a patient coming east from North Adams. Soon after leaving the station, she was seized with agonizing abdominal pain accompanied by vomiting. The train stopped at Gardner. Dr. A. F. Lowell had the patient transferred to the Heywood Memorial Hospital. After examination there he believed her severe symptoms were caused by a ruptured ulcer of the stomach and advised immediate operation. Dr. Lowell conferred with me by telephone. In reciting the history he stated that the patient had never suffered from symptoms suggesting the previous existence of peptic ulcer. He noted also that muscular rigidity was almost entirely confined to the upper abdomen and that there was a somewhat indefinite tender mass in the epigastrium. Knowing that Dr. Lowell was a careful and competent surgeon, I concurred with him in the belief that the patient should be operated upon without delay, adding that in a case of this type one should have acute pancreatitis in mind and a careful search should be made for the pinhead areas of fat necrosis, which is the pathognomonic sign of the disease. He called me back about two or three hours later and said, "I found the little white spots, and merely drained the gallbladder." The patient recovered. This happy result was due to the fact that the operation was done within a few hours of the onset of the attack when a simple procedure was safer and more effective than a radical operation if done 24 hours later.

THE PUBLIC AND OUR PROFESSION*

BY EDWARD H. CARY, M.D.†

TODAY, I come as the president of the American Medical Association to speak to you of what this organization has meant to us in a social, material and spiritual sense. I shall also call attention to the importance of this great medical association to the people whose health and happiness is the result of constant vigilance on the part of the members of our great organization.

The progress of the science of medicine has been accomplished in a most orderly manner. It has been directed and purposely guided in research and distribution of knowledge, and through its activities there has been an esprit de corps developed in the rank and file of medical men throughout the United States. Knowledge possessed by a member is quickly publicized after it has been presented to confrères in open forum. Our association develops new ideas, new truths, or maybe old truths further illumined. It stimulates and captivates the minds of our fellow workers.

A great community interest encourages the individual doctor and sharpens the competition for him, because the people are free to choose those who can retain and best use the information acquired. This is made possible for all the people because of the activity and orderly force created and kept alive by organized medicine.

If we are to interpret properly the attitude of the medical profession by its behavior during this period of general distress, it is helpful to review some of the strata underlying the medical structure. With this in view, I shall attempt to present some of the related causes of medical opinion.

It is interesting that, of all of the associations of men that for centuries have bound themselves together for a common purpose, the profession of medicine is the only one which has grown stronger and more dignified through the years. It has survived as an entity because of the basically sound policy of the free distribution of knowledge, imparted by its members each to the other, for the purpose of serving the human race. The improved technique has become the property of all who cultivate the art and science of medicine; thereby society is benefited.

Medicine readily becomes an instrument of the brotherhood of men who are engaged in properly interpreting Nature's secrets. Medicine, both a science and an art, is gloriously stimulating for it lays bare the gamut of human emotions. The science of medicine bridges human eccentricities, and all ethnological circumstances.

Disease affects individuals differently, depending upon the immunity acquired. Cellular reactions in human beings, when observed and recorded, represent widespread experiences.

The true scientist develops a certain quality of mind, for while delving and searching for gems of truth, his mind becomes attuned to Jehovah's purposes. The patient worker builds a pathway with fact after fact honorably placed for the pageant of civilization to mount upward and onward. Sometimes the builder is not well known and remains unsung regardless of nationality. His own reward is a glimpse of God expressed in the infinitely small, or maybe, in the infinitely great.

Conjecture as you may, we believe that this is a real reward for men who toil in every nation of our far-flung universe, for they are interpreting facts, and constructing the "Roadway of Truth."

Medicine has had its allies, both in the men who developed the basic sciences and those who rightly interpreted them. Open minds with ready wit and a capacity to inform the world through literature, as did Voltaire, Franklin and others, quickened the acceptance of scientific truths as they were developed.

The science of medicine, as we know, gained its greatest impetus with the discoveries which rapidly followed the work of Pasteur and Koch, who revealed the heretofore invisible but important factors of life to an astonished world. From that time on, the etiology of disease could be proved experimentally, and as one discovery after another of the causes of recognizable diseases became known, medicine lost much of its superstition and developed true scientific merit.

The thirst for knowledge became the ruling factor in medical education and this incentive is the binding force which underlies the progress of the medical profession.

The Law of Hippocrates has been a determining factor in holding physicians to ethical standards, for it expresses particularly the nobility of the art and emphasizes the necessity of avoiding ignoble practices. The Father of Medicine has made it possible for us to adjust the practices of tomorrow by using the yardstick of his tenets to measure the conditions of the modern world.

Suppose we now turn our attention to the influence of modern conditions upon material and ethical problems in medicine as we find them today. We cannot ignore the higher cost in time and money necessary to create competent physicians. The modern medical man is confronted with an ever-growing science which often develops more rapidly than he can encom-

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†Cary—President, American Medical Association, June, 1932, to June, 1933. For record and address of author see "This Week's Issue," page 109.

pass the art of medicine as expressed in its practice.

Today we face an ever-increasing army of modernly educated physicians, most of them seeking to discover through research in laboratories and clinics the cause of disease. This vast army is ready to apply acquired knowledge to prevent the recurrence of disease which engages its time and brings a livelihood. We recognize already a lessening demand for our profession. Preventive measures as applied by physicians have eliminated many diseases which once occupied the profession's attention. Sanitary laws and immunization, the result of professional knowledge and agitation, are rapidly making life safer in all localities, a contribution so great that the people now think of the state of the benefactor instead of the medical achievement. Medicine is not the result of chance; it is the product of many minds deeply interested in human beings.

It would be inconceivable for the medical profession to fulfill its high task in the service of humanity if it were not working as an organization, having fixed principles to guide it. The people should know this, and if they were properly advised they would sustain any effort on the part of medical men to build a strong, responsible Association, for it conserves the health of the people.

Nothing should be permitted to destroy harmony of action within the profession. The well-being of humanity is intimately associated with the high ethical concept adopted and preserved by the medical profession to sustain its own nobility and its interest in the people's welfare.

Eliminate the application of accurate medical knowledge through ill-considered economic practices to the conceivable point of diminishing monetary return, and medicine will, in a large measure, become an abstract science, valued as an intellectual pursuit, but deprived of an important human incentive, which incentive has so definitely made the science and art of medicine serviceable to humanity.

Today society is so complicated that if medical knowledge lagged or ceased to progress, it is conceivable that society, as we know it, would wane and the human race be left to struggle with the recurring pestilences of the past. Education and ethics, the great motives underlying medical organization, furnished the cementing force which unites men to a common purpose. This purpose has always contemplated the welfare of the human race.

In 1902, the American Medical Association was organized as a modern expression of the sentiment which has held medical men together as a body throughout the ages. Medical men believe in the elevating quality innately existing within the profession. Seemingly it is true that the educated physician in any age has been a superior man. Though exact scientific knowledge may have been lacking, there has always been something ennobling in the study and the traditions of medicine, which caused men to catch the real vision of life's values. There was simple living and high thinking. There has been orderly evolution in the construction of the roadway of scientific fact.

An organization such as the American Medical Association must necessarily have a code of ethics, and although our code is the outgrowth of tradition, it is a modern expression of our desire to relate our interests to those of the people, and to serve the people in a uniform manner. It does not abridge the rights of any man, and as a living manifestation of ethical restraint it can be viewed triumphantly, for the golden thread of moral and spiritual values can be traced through all medical history.

Conservatism is a normal view of the average practitioner. Any change in method of practice is resisted until it becomes clearly apparent to the majority in a locality that change is necessary. Social trends may be recognized and yet the medical man will be slow to adopt new methods. Such conservatism is normal and, in the broadest sense, is probably for the good of society.

If it be true that society is best served by a great profession not easily swerved from its ideals and mode, then society should be willing to have any proffered plan to revise medical practice thoroughly discussed and made genuinely sound before a radical change is adopted. The time necessary for a solution should be conceded by society.

Organized medicine believes that it has several definite functions. First, and most important, it must practice medicine; and when this is said, actual contact with individuals who are sick is meant.

Influenced by economic urge, any mechanism which tends to destroy the intimate relationship between the doctor and patient, will find its reflex in disturbed professional service, destructive to human satisfaction.

We believe that as an organization it is our duty to protect individualism in the practice of medicine, and it is wholly logical for us to resist socialization of medicine from any source.

We readily perceive, however, that there are superficially informed persons who would have medical men less individualistic. They would place them in groups under a leadership, lay and professional, which would tend to destroy the right of self-determination in the practice of medicine. We believe such a condition would lessen initiative and develop a tendency to mechanize medicine. If so, the contact of patient and doctor would become less intimate and the true story which every patient wishes to tell, would remain, in many instances, unrevealed. In harmony with Schwitalla, I may say

that no one should stimulate a movement toward coercing medicine through social stress as an economic need. It is fallacious to believe that an organized group is immediately endowed with the extraordinary capacity. It depends, after all, upon the members comprising the group, and the amount of individual attention given the patient by the individual doctor, who should be deeply and personally interested. This function can be performed in or out of a group. While medicine has to adapt itself to human needs, we must not lose sight of the first law of nature, which is self-preservation.

Because doctors have felt that healing the sick is a sacred trust, because the very nature of their work requires that they put their time, their strength, their skill and their very life, at the call of humanity, they cannot view with comfort the prospect of a radical change in their present plan of practice. No one knows better than the doctor the need for an intimate understanding of the patient's background. To obtain this information, the physician must often become the possession of the sick individual. The medical profession cannot be mechanized until human beings become machines.

We also believe that it is the function of organized medicine to promote preventive medicine and public health work; primarily this we also believe, is the function of organized medicine to promote preventive medicine and public health work; primarily this means the education of the public. Though statements to the contrary have been made, there has been an abundance of medical leadership deeply interested in magnifying public health measures. Through the units of our organization and our state medical associations, all of the information believed to be acceptable to the public is being constantly and systematically given to the people through professionally supported public health agencies, and by doctors who make popular health radio talks, and through thousands of articles given to the press. All of this is in the interest of public health in an effort to prevent disease.

The American Medical Association early in its career had among its members a few medical statesmen who planned wisely for us. Those of us familiar with the work of our councils and bureaus, not only in education, but in pharmacy and chemistry, and many kindred departments, recognize the far-reaching influence these councils have had in the protection of the people through higher standards in medical education, pure food and drug laws, and the standardization of pharmaceutic preparations.

Pseudoscientific claims, paraded as cures for some of the most serious diseases which affect humanity, are not so boldly exaggerated today as formerly. A well-recognized human trait is optimism, and there are few persons suffering with a chronically fatal malady who will not believe the most improbable promise of cure.

To combat the vultures who are perfectly willing to prey upon humanity has required more courage and money than the average or small medical society could afford. The American Medical Association has assumed this task and utilizes its knowledge, its accumulated monetary surplus, and its determination to save human beings from such exploitation. Of the numerous suits for libel, tried at a cost of thousands of dollars to the Association, not a single case has been lost. Such protection for the profession and the public is invaluable. Boldly pursuing this policy we make it possible for the secular press to condemn evil practices.

Another function of organized medicine is to foster research and, through new discoveries, increase our knowledge. Research has definitely been encouraged. The American Medical Association provides money for grants which some three hundred workers are now using. To further this phase of endeavor, our organization is well supplied with journals of the first rank.

In magnifying the advantages of the practice of medicine, we have attracted a far greater number of the highest type of young people than can be assimilated at this time. This year, which brought much in educational accomplishment, has evolved material changes in economic values, both in urban and rural sections, creating a mutual problem for the physician and the people.

The number of medical graduates, plus those who come from abroad, now exceeds the mortality of our profession in numbers sufficiently large to be alarming as to the matter of distribution. We recognize the curtailment in population, due probably to artificial barriers interposed both in home life and in restricted immigration laws. This economic problem would seem to be of equal gravity to the medical body and to the public.

Any retardation in distribution of proper medical service in communities is not necessarily the fault of the medical profession. It is more often a characteristic social phenomenon which has always existed. Though this may be a fact, it does not preclude at this time an endeavor on the part of the medical profession to make available its knowledge which could be more widely used. We are willing to coöperate with far-seeing citizens who have become leaders in social welfare activities, in making an attempt to solve the economic necessities, with justice for the physician and adequate medical service for the people.

Adjustments are more necessary now than heretofore; the incidence of diseases so prevalent a few years ago has decreased, some of the diseases have been entirely eliminated, which fact has accelerated the movement of physi-

cians to cities, and the ever-increasing number of specialists. The public has been educated to the value of the applied sciences. Medical practitioners find their clientele frequently looking to the public health authorities for preventive measures and services which the practitioner should perform. It has been said that this is largely the result of a lack of interest on the part of the profession.

The Commissioner of Public Health in Detroit, Michigan, is intelligently using the medical profession in his work. He has awakened the profession to the importance of the prevention of disease, which has been of decided advantage to the general public in Detroit, as well as to the physicians involved. He has made of each doctor's office a community health center. Public health officials should likewise coöperate with the leaders of the medical profession in various localities.

Not only forty per cent, but eighty or ninety per cent of the children in a community should be immunized against those diseases for which we have preventive measures. This can never be accomplished by the public health authorities without great detriment to the medical profession, unless the two forces coöperate.

It is generally recognized that good health is one of the important necessities of life. With physical vigor, a people may be happy, and through contentment one might visualize prosperity. Dependency and unemployment often follow in the wake of sickness. Since health in a measure can be purchased, we must realize that a country which habitually attempts to regulate its industries, and has developed universal education at the expense of the people, is likely to make an effort to conserve and improve their health, through similar regulatory measures.

It remains to be seen whether the medical profession will broadly provide the leadership to guide and direct this social trend. The economic situation at this time has stimulated a widespread interest in evolving a plan to meet the present condition. Though it is obvious that methods must be devised and previous ideas of medical care adjusted, we must not lose sight of the fact that social needs today are more extreme than we anticipate for the future. However, we recognize that it is our duty to mobilize the best current scientific knowledge for the benefit of the individual in the community.

The public is unaware of the extraordinary amount of labor and time, with monetary outlay, required to equip men and women for medical service. I dare say the public knows little of the risks and uncertainties of medical practice, and the expense of maintaining proper facilities for carrying on. Do they ever think that their doctor may lose his health and be deprived of his income?

The average physician is frequently confronted with an economic problem which makes the practice of medicine precarious. It is clearly the duty of organized medicine to check the growth of community programs for medical service which undermine the financial stability of the individual physician. We concede the ideal that every family should have 100 per cent of needed medical service. We recognize that families with annual incomes under twelve hundred dollars receive but approximately 33.3 per cent of needed health care, and while those of greater amount receive correspondingly more medical service, it will require the coöperation of an enlightened citizenship with a willing profession to develop plans suitable to the needs of a given locality. Many county medical societies are experimenting with various ideas with this in view. Any plan, to be successful, must be inclusive in character as regards members of the county medical society, permitting the patients to budget their needs.

There must be some plan provided whereby prolonged illness requiring medical service or needed surgical procedures, will not become a catastrophe. Out of the many plans being tried and widely discussed, we may hope to crystallize medical opinion around feasible principles, recognizing that no one plan can meet all conditions in different localities.

Haggard has wisely intimated that medicine, as it grew to be more scientific, lost much of its charm for the people, for as an art and not a science, it appealed to the emotions. It seems to be inconsistent to make progress in the sciences and stimulate reverence or adoration.

As we have grown more scientific, whether as doctors or engineers, our contributions are accepted and utilized, but we fail to stimulate the imagination and primeval devotion in the individual, which suggests that the art of medicine has declined.

Cultism has thrived in proportion to the lack of interest of physicians in utilizing artistry in the practice. When we think of approximately five hundred million dollars spent annually on self-medication and cultism, by the people of this country, it seems to us fundamental that the profession of medicine as now practiced is likely responsible for a very large proportion of this waste, as well as the harm done, which in many instances, is irreparable.

It is not enough to know the cause of disease which affects a patient; there must be sufficient interest on the part of the doctor to make the patient accept his knowledge and advice.

To hold the people as our friends, we must reincarnate the family physician with his sympathy, homely philosophy and heart-felt interest, that he may again animate the practice of medicine. It has often been said that 85 per cent of the medical needs can be cared for most economically by the family practitioner.

The report recently released by the Committee on the Costs of Medical Care, is significant,

for it is based upon certain concepts of society and functions of government. As a nation, we have been developing governmental control to meet social demands without having a definite policy.

The great war left its quota of disabled. It seemed both wise and just to care liberally for the casualties, which was enthusiastically done. Without establishing a definite policy to care for claims which come in the wake of war, Congress yielded to the demands of a group of citizens for broader concessions. From that time on, hospitalization and compensation, with many other far-reaching governmental services were exploited. Social welfare forces became enthused and rapidly evolved plans which became highly suggestive of a more liberal aid for all the people.

At this juncture, the economic situation throughout the country became a paramount issue. While some of us were laboring to create a new policy toward the hospitalization of the non-service disabled veterans, there were other groups, ably represented, attempting to get the government out of business and to force economies which would be far-reaching in effect.

Our profession was represented at the same time before a Joint Committee of Congress, and the medical opinion on these matters was presented. With the change in administration, a courageous leader has been given the power to revamp not only the pay of the government officials but to eliminate vast numbers of gratuities which should never have been allowed. This means that the government will not build contemplated hospitals, for which there have been appropriations but which have not been started. It means the closing of many hospitals now in use, but not well located. It means the opening of some new hospitals which are in process of construction. It means that the non-service disabled veteran, able to pay, will not hereafter become a governmental responsibility. Government hospitals will be utilized for the care of service-disabled veterans, mental and nervous cases, and those veterans afflicted with tuberculosis. Inasmuch as it has always been the government's policy to provide homes for the old soldiers, it is contemplated that the present government hospitals will be used more and more for domiciliary care.

The problem of governmental hospitalization has disturbed the medical profession because it was generally believed that, if not halted, such hospitalization was destined to lead our nation into state medicine. We must be alert to prevent a recurrence of this menace, and not assume that the same forces will remain inactive.

If our country should become prosperous before the present government plan can become a fixed policy, the whole question will be reopened. In Congress, approximately twenty-five claims a day are being presented for pensions, regardless of cause of disability. We are not through with such indulgences.

Accumulated data have clearly emphasized the importance of medicine as relates to social needs; such data clearly support our present educational standards. Everyone realizes that there can be no one answer applicable to the varied conditions, social and economic, because conditions change in different environments.

In reply to the suggestion that medicine become more adaptable, Schwitalla has said, "That paradox of adaptation lies perceptibly in this: that a measure of isolation spells a continuation of life; exaggerated adaptation means death."

A biological truth to be remembered! He also said, "The organism which adapts itself to its environment with restraint due to self-contained inertia, survives."

The statement has been made that the medical profession of this country has been denied valuable information which is being developed and which is out of harmony with the view expressed in the Minority Report of the Committee on the Costs of Medical Care and elaborated in our own medical journals. I feel that we can deny this charge!

The reaction of the leaders of our organization to the report has been very much the same, and if one cares to investigate, it would be found that the profession throughout the country, has responded in a similar vein. There is nothing more natural than the desire of a great profession to resist change until it has had sufficient time to adjust its mind, if that time should be needed.

The impatience of some of the leaders engaged in social welfare work to hurry the profession to a decision, even going so far as to threaten us with a definite campaign of propaganda to influence the public, is worth noting. I am one of those who believes that it is wise to utilize enough time to crystallize our opinion. The public should recognize that physicians are better able to solve medical questions than anyone else, and that lay opinion, however suggestive and valuable it may be, lacks finality and that essence of true understanding of a doctor's relationship to his patient.

Our organization is striving, through its leaders at headquarters and elsewhere, to serve the public and the profession of medicine, first by discussion of problems, secondly, by trial of suggested plans and thirdly, by searching for and finding the truth. Thus will we be able to crystallize the professional mind so that unity will prevail. We all recognize that until there is unity of spirit and professional desire among the members of county medical societies, which are the basic units of our organization, no plan, however far-reaching and humanitarian in its aspects, can hope to live without the coöperation of the majority of physicians practicing in the locality covered.

Medicine of all the arts, is the most exacting. It is a jealous master of the time, opportunity, and capacity of those devoted to its service. In pursuit of the underlying sciences, the art of medicine has sometimes been neglected. It is also true that sequential knowledge, culminating in the large field of sociology and psychology, has become known to an ever-widening circle of humanity.

To adjust the science and art of medicine to the satisfaction of this educated and expectant mass of socially conscious people, will not be difficult when the members of our profession unify their desire to lead those minds which want to control and direct the practice of physicians.

Regardless of our numerous and valuable associations, doctors throughout the country should recognize their need for a strong and militant national medical organization. It is the only body which can truly claim the loyalty of every worthy practitioner. It can concretely express the aspirations and purposes of every follower of Aesculapius who believes in the fundamental principles of ethical medicine.

The American Medical Association has won the respect of its members and informed society. It has been faithful to a trust. Let us give it our unswerving allegiance.

Dignity and economic fairness, as well as conscientious scientific service, depend upon the unity of the medical profession. Ethical standards have held. We have remained true to an ideal. Every appreciative man within our profession realizes his obligation to those who have left a wonderful heritage.

If this organization of ours should fail, medicine as we know it would disintegrate; and if this should ever come to pass, my friends, who would suffer more than the people who have learned to respect and trust us?

Medicine must be dynamic; it must be amenable to change in policies as conditions dictate, but change is not always advancement, and medicine must use its best wisdom in making changes, that sound, progressive policies, be adopted.

Medicine may properly establish rules of conduct for its members, but these rules can only be successfully maintained when they correspond to sound ethical principles.

In its ethics, medicine, considering its own affairs, has essentially three purposes in view: to inculcate ideals; to provide conditions of practice in which there is fair competition among practitioners, and to give opportunity, as unrestricted as possible, for individual development.

May I refer to a report made by Doctors Pusey, Follansbee, Sargent, Leland and Cary, at the Conference of State Association Secretaries last November. Although our committee attempted to elucidate many points bearing upon present-day ethical relations, too numerous to recount here, the report was, after all, but a restatement of ideals and gentlemanly conduct, as old as the law of Hippocrates and restated to meet the complexities of our time, being the results of technical changes which are sequential developments of material progress.

The medical profession treasures its ancient home of Hellenic origin. Its straight lines reflect beauty. None of us complain of its architecture, but as time goes by, like all homes, it needs repolishing. Its superstructure stands upon a foundation which time has scarcely marred. The builders of today, like the builders of yesterday, are trying to keep this foundation sound and secure. The portals of this home have always been flung ajar, to extend gracious hospitality to those who need its beneficent bounty. We are proud to claim it as our habitat, and we should protect its beauty, culture and integrity with our lifeblood.

So my friends, when invited to speak to you on this occasion, I chose the subject "The Public and Our Profession." I have endeavored to direct your attention to the value of this great organized profession in the present situation.

In conclusion, I point to the home of our Medical Fathers, wherein their spirit dwells; the readjustment of the present with the past, a clear understanding of society's needs and our usefulness to it, with the abiding thought that, through coöperation and education, the science will progress and its art in the practice of the science will be preserved as an individual blessing for each of the needy souls requiring its ministration.

MISCELLANY

RECENT DEATH

WATSON — GEORGE MARSHALL WATSON, M.D., of Manchester, died at his home December 13 at the age of 65.

THE ASSOCIATION OF DIABETES AND TUBERCULOSIS*

II. Pathology and Etiology

BY HOWARD F. ROOT, M.D.†

A. Pathology

1. Preface.
2. Series of autopsies.
3. Incidence of active pulmonary tuberculosis at autopsy.
4. Types of pulmonary tuberculous lesions.
5. Extrapulmonary tuberculous lesions.
6. Non-tuberculous pathology.
7. Causes of death.
8. Quiescent and healed lesions.
9. Comparison with tuberculous lesions in non-diabetics.
10. Tuberculosis in the Negro and diabetic.

B. Etiology

1. Bacteriology of tubercle bacillus.
   a. Variation in form.
   b. Cultural and metabolic characteristics in relation to diabetes.
   c. Virulence.
2. Immunity of the diabetic.
3. Allergy and resistance.
4. Contagion.
5. Summary.

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1) PREFACE. For a study of the pathologic changes found at autopsy in cases of combined diabetes and tuberculosis, the records antedating 1900 are of comparatively little value, and unfortunately even in recent reports details are not profuse. One is forced to conclude merely from the lack of statements to the contrary that the microscopic appearances of tuberculosis as found in the diabetic show no peculiarities which would distinguish it from non-diabetic tuberculosis. The distribution of tuberculous lesions, the frequency of certain of its forms, the rapidity of its course and the ages of the patients have been the most frequent subjects of comment.

2) SERIES OF AUTOPSIES. In table 1 are included five series of diabetic autopsies in which evidences of healed or active tuberculosis were found. The selection of these series was dictated by the fact that either some details were given as to the clinical and diabetic records or else that sufficient data were given regarding the lung findings and the extrapulmonary findings to enable some conclusions to be drawn about the types and locations of tuberculosis. The older reports of autopsies are for the most part merely reported in summary. Even the series of Naunyn[1] includes patients autopsied in the latter part of the 19th century. Such a series cannot be compared with autopsies performed upon patients dying since 1918 with respect to the incidence of tuberculosis owing to the tremendous change in social conditions and in the types of hospitals which now allow for much greater segregation and isolation of tuberculous patients than was formerly the case. However his series may be used in considering the types of lesion found within the lungs.

a. The first 15 autopsies were performed at the New England Deaconess Hospital, Boston, Massachusetts since 1923. The Deaconess Hospital takes private patients mainly and the series represents elements in the population as a whole which might be absent from a series drawn exclusively from the wards of a public or municipal hospital where the patients were for the most part from the unfortunate and from the crowded districts of the city. Thus, there are only 7 cases of tuberculosis causing death in 150 autopsies, 3 with small active lesions not the cause of death, and 5 with healed lesions.

b. Sauerbeck's[2] series belongs to an older period. No details are given as to the type of pulmonary tuberculosis although it seems evident from his article that the pulmonary tuberculosis was probably the cause of death. The series is included because he gives descriptions of the pancreas and particularly of the islands of Langerhans.

c. Naunyn's[1] series is taken from 49 autopsies apparently performed in the great public hospital in Strassburg prior to 1906. These series, however, should not be included in any comparison of diabetic and non-diabetic autopsies done in the last ten or twelve years.

d. Pagel and Henke[3] report two series of autopsies. The first is from the Pathologic Institute of the University of Berlin consisting of 101 diabetic autopsies performed since 1918. It includes 15 cases of active tuberculosis and 13 cases classified as inactive and non-advancing. The second series of 40 cases is taken from 164 diabetic autopsies at a large hospital in Friedrickshain near Berlin.

e. Montgomery's[4] series of 7 cases from Philadelphia was described in 1912.

f. Dr. Shields Warren has given me 10 cases

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The coöperation of Dr. Gerald B. Webb, and the financial assistance provided by the Colorado Foundation for Research in Tuberculosis and the Chemical Foundation, New York, are gratefully acknowledged.

†Root—For record and address of author see "This Week's Issue," page 109.

TABL

126 AUTOPSIES UPON T

A—Deaconess H

Case No.	Age Onset Diabetes	Age Onset Tuberculosis	Age At Death	Sex	Pancreas: Size Grams	Pancreas: Islands of Langerhans Hyaline	Pancreas: Islands of Langerhans Sclerosis	Pancreas: Acinar Sclerosis	Arteriosclerosis	Lungs
177	44	?	76.3	M	90	Few +	Fatty		++++	Left upper lobe contains cavity and
1977	70.9	?	81.2	F	75	Few +	+	Calculus + ++	+++	Nodules with caseation both apice adhesions.
3176	41.2	53	58.5	M	Normal		+++	+	+	Tubercles and areas of consolidati Large cavity in right upper lobe
6791	40.1	?	41.5	M	70	Small	+	++	++	Nodules throughout all lobes. Cavit and lower lobes right.
6809	31.8	32	33.4	M	90			+	+	Nodules throughout all lobes both lu lobes contain cavities.
7041	6.3	14.1	14.8	M	40	Few	+		+	Double pneumothorax. Numerous cles and areas of consolidation i
11471	44	48	48	F		+	0	0	++	Cavity right upper lobe. Gelati throughout right lung. Ossified mary focus.
1257	55		78.1	F	30	++	++	++	+++	Bilateral apical scars.
3134	64.3	?	73.8	F	90	++++			+++	Bilateral apical scars.
3901	44.1		55.8	F	70	++		++	++	Few tubercles at apices.
4284	61.4	?	71.5	M	100	+	++	++	+++	
9013	60	?	64.7	M	110	+	++	++	++	Healed apical lesion.
9731	75	?	76	M	60	Numerous			++++	Large area scar tissue both apices abscess right lower lobe.
9853	64		64.3	M	110	Cancer		++	++	Scar tissue both apices. Right midd calcified area of caseation.
4862	57	?	64.8	M	Normal				+++	Healed apical lesions.

B—Other

Author	Age at Onset D. M.	Age at Death	Sex
	Yrs.	Yrs.	
Sauerbeck			
1	70	70	F
2	25	27	M
3	41	43	M
4	71	73	M
5	54	54	F
6	29	29	M

Author	Age at Onset D. M.	Age at Death	Sex
	Yrs.	Yrs.	
Naunyn			
5	31	32	M
11	?	45	M
12	10	10	F
14	7	8	M
15	56	56	M
16	35	36	M
17	42	45	M
21	14	17	M
23	34	36	M
27	?	27	F
31	?	58	M
34	46	48	M
35	44	50	M
36	32	33	M
39	10	12	F
40	26	33	M
42	66	74	M
43	?	33	M
44	38	38	M
49	30	31	M

Author	Age at Onset D. M.	Age at Death	Sex
	Yrs.	Yrs.	
Warren			
1	41	43	M
2	43	47	F
3	43	45	M
4	38	40	M
5	45	48	M
6	27	28	F
7	23	23	F
8	28	28	F
9	56	58	M
10	56	57	M

Author	Age at Deat
Pagel and Henke	
1	26
3	31
4	52
9	?
10	56
18	23
21	44
24	33
28	62
30	25
38	46
40	55
42	57
46	26

ABLE 1

Tuberculous Diabetics

ss Hospital Series

Tuberculosis		Com
	Other Organs	
and many tubercles.		Acute infarction Nephritis. Abs
pices. Old pleural	Caseous mesenteric glands.	Peritonitis.
idation in all lobes. lobe.	Fibrinous pleurisy.	Fibrous myocarditi
avities in both upper	Caseous hilum and mediastinal nodes.	Gastric ulcer.
h lungs. Both lower	Many ulcers in intestine.	Gangrene. Chron sclerosis.
ous cavities. Tuber- on in all lobes.	Intestines. Pleurisy. Tracheobronchial and mesenteric glands. Liver miliary.	
elatinous pneumonia ified subpleural pri-	Ileum, liver, spleen and lymph nodes.	Gall-stones.
		Coronary thrombos ulcer.
		Chronic nephritis.
		Infarction of hear
	Calcified mesenteric node.	Cerebral hemorrh lungs and brai
		Vegetative endocar
pices. Encapsulated		Periurethral absce
middle lobe partially		
		Fibrous myocardi heart. Cirrhosis

ther Series

Age at Death	Sex
26	M
31	F
52	M
?	?
56	M
23	M
44	M
33	M
62	M
25	M
46	F
55	M
57	F
26	M

Author	Age at Death	Sex
Pagel and Henke		
48	32	M
55	49	M
56	17	M
57	32	F
61	39	M
63	46	M
65	63	M
75	62	F
81	53	F
85	64	F
88	75	F
96	56	M
99	65	M
100	78	M

Author	Age at Death	Sex
Montgomery		
1	51	M
2	27	M
3	21	M
4	58	M
5	32	M
6	33	M
7	45	M

Complications	Cause of Death
rction of heart. Cholelithiasis. is. Abscess of prostate.	Gangrene.
	Pulmonary tuberculosis.
vocarditis.	Tuberculosis.
er.	Pulmonary tuberculosis.
Chronic nephritis. Coronary s.	Bilateral pulmonary tuberculosis.
	Pulmonary tuberculosis.
	Tuberculosis.
hrombosis. Perforation duodenal	Coronary thrombosis. Perforation duodenal ulcer.
phritis.	General arteriosclerosis, cerebral edema.
of heart. Cholelithiasis.	Coronary thrombosis.
hemorrhage. Infarcts of heart, nd brain. Nephritis.	Cerebral hemorrhage.
endocarditis. Multiple emboli.	Ulcerative endocarditis.
al abscess. Intracardiac thrombus.	Embolism.
	Cancer of pancreas.
nyocarditis. Multiple infarcts of Cirrhosis of liver. Gangrene of foot.	Coronary sclerosis.

Author	Age at Death	Sex
Pagel and Henke No. 2		
1	56	M
2	60	F
3	31	M
4	60	F
5	49	M
6	58	M
7	58	F
8	62	F
9	65	M
10	76	F
11	34	M
12	53	M
13	75	F
14	?	F
15	18	M
16	62	M
17	24	M
18	42	F
19	57	M
20	22	M

Author	Age at Death	Sex
Pagel and Henke No. 2		
21	20	M
22	64	M
23	22	M
24	45	M
25	65	M
26	67	F
27	27	M
28	23	F
29	67	F
30	51	M
31	55	M
32	48	M
33	56	F
34	14	M
35	68	M
36	27	M
37	39	F
38	62	M
39	65	M
40	73	F

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from the series of 283 diabetic autopsies analyzed by him in 1928. These cases were from the Peter Bent Brigham Hospital and City Hospital in Boston and from Lakeside and City Hospitals in Cleveland, Ohio.

3) Incidence of Active Pulmonary Tuberculosis. For a comparison of the incidence of tuberculosis in diabetics the series from the Deaconess Hospital is of little value since patients known to have active tuberculosis are not admitted, and those in whom it is discovered are transferred to tuberculosis sanitaria as quickly as possible. Therefore, deaths from pulmonary tuberculosis represent cases with a terminal illness, too sick to be moved, or occasional cases admitted for surgical treatment of some complication. I am not certain whether this would hold true with the Pagel and Henke series of 265 diabetic autopsies in which 55 cases of active tuberculosis were present, an incidence of 20.8 per cent. Fitz[5] reported from the Peter Bent Brigham Hospital whose autopsies were performed since 1914, that pulmonary tuberculosis was found in 19 per cent of diabetics. These figures may be compared with the non-diabetic series of Ophuls[6] who has analyzed 3000 autopsies from the Leland Stanford Hospital in San Francisco. His autopsies also belong to the modern period. He had 530 cases of active pulmonary tuberculosis or 17.7 per cent. The incidence, therefore, of active pulmonary tuberculosis at autopsy at present seems to be only slightly greater in diabetics than in non-diabetics, and is distinctly less than was found in the older series prior to 1900. Nevertheless, this indicates that pulmonary tuberculosis complicating diabetes is found at autopsy between 2 and 3 times as frequently as would be expected, if the conclusions of Carlson and Bell (*New Eng. J. Med.* 210:2, 1934) be accepted.

Sex. There are 89 males and 36 females, sex unrecorded in 1. The sex distribution is nearly that of tuberculosis in the community and in strong contrast to the sex distribution of diabetes, which approximates 50 per cent for each sex, although the percentage of females has steadily increased since 1900. If diabetes had exerted any very marked influence in the development of tuberculosis, one would expect a sex incidence tending toward that of diabetes. This may appear later, if the prolongation of life due to use of insulin permits the development of more tuberculosis.

Age. In table 2 are summarized the ages at death of 123 autopsied cases. Diabetes is not so rare in youth as was once thought. In fact at least 10 per cent of the cases have their onset in childhood and 50 per cent before the 50th year. One might expect, therefore, that a relatively large percentage of the total deaths from tuberculosis among diabetics would occur in the earlier decades. However, the peak was not reached until the decade from 50 to 59 years and 58 out of 123 deaths occurred after the age of 50 years. Similarly among 161 deaths in the Deaconess Hospital tuberculous diabetics, only 11 occurred before the age of 30, while 74 occurred after the age of 50 years.

It would be desirable to compare the age at onset of tuberculosis with the age at onset of diabetes, but the data are not sufficiently accurate. In one of Naunyn's cases, data are given which showed clearly that the patient had had tuberculosis 9 years before the onset of diabetes. In the 245 Deaconess Hospital cases, in 207 instances diabetes was regarded as having preceded the tuberculosis.

TABLE 2

Ages at Death of 123 Autopsied Cases Combined Diabetes and Tuberculosis

Decade	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79
Number	1	7	19	19	19	24	20	14

The primary infection undoubtedly occurs early in life in the diabetic. The time of development of the secondary pulmonary tuberculosis is difficult to establish. In general it is known that tuberculosis not only in diabetic but also in non-diabetic patients may advance during a period of months or years with no clinical symptoms. It is much less likely that diabetes will be present for a period of years without giving evidences by characteristic symptoms or by a routine urinalysis. The more carefully our histories are examined the more frequently it becomes evident that pulmonary tuberculosis had existed months or years before the present flare-up. Nevertheless it is clear that in the great majority of cases active, progressive tuberculosis, when present, developed after the diabetes.

4) Types of Pulmonary Tuberculous Lesions in Diabetes. Although a total of 126 autopsies are included in table 1, a considerable number are suitable only for limited discussion because of insufficient data. Thus in 14, although pulmonary tuberculosis was stated to be present, no details as to its character or extent are given. In 50 cases the pulmonary lesions are merely described as "productive" or "ulcerative". It must be admitted that the total number of autopsies is so small in comparison with the large number of non-diabetic autopsies that conclusions must be drawn with reserve. In fact, one is almost forced to conclude that so far no individual has studied a sufficient number of autopsies to justify any comparison of diabetic with non-diabetic tuberculosis.

This series is therefore discussed with frank realization of the limitations imposed upon inferences or comparisons with non-diabetic tuberculosis.

a) Healed tuberculosis. In eight cases of this

series only healed processes are present. The duration of the diabetes as well as age at death are known in the Deaconess Hospital series. Case No. 1257, female, aged 78 years, is notable in that her tuberculosis remained healed in spite of having diabetes for 25 years. Case No. 3134, female, aged 73.8 years, also exhibited bilateral scars in both apices after diabetes of 4.5 years. Case No. 4284, male, 71.5 years, and Case No. 4862, male, aged 64.8, both with healed apical lesions had had diabetes only 4.7 and 7.8 years, respectively. Pagel and Henke's case No. 28, male, 62 years, had a calcified focus at the right apex. In contrast to these aged patients, Pagel and Henke's Case No. 3, female, aged 31, is described as "not active."

The proportion of cases with healed lesions in relation to cases with active lesions is so extraordinarily small as to indicate clearly that only frank, outspoken healed lesions have been noted. Small areas of pleural thickening, pleural adhesions, small calcified foci must have been disregarded. That the occurrence of healed tuberculosis in diabetics is really infrequent must not be inferred from these figures. We believe that tuberculous infection in diabetics is just as frequent as in non-diabetics (as indicated by the von Pirquet or Mantoux tests in childhood) and that the x-ray evidence of calcification in tracheobronchial glands and in small foci within the lungs, found in 70 per cent of our diabetics in the Deaconess Hospital has the same significance as indicating healed or healing tuberculous lesions as in non-diabetics.

b) In only 56 cases of this series are the pulmonary lesions described in such detail as to leave little doubt as to the presence or absence of cavitation. Of these, 28 had cavities, an incidence of 50 per cent. Single or multiple cavities occurred in upper or lower lobes. Large cavities were present in 3 children out of 9, Deaconess Hospital Case No. 7041. boy 14.8 years, Naunyn's Case No. 21, boy, 17 years, and Naunyn's Case No. 30, boy, 12 years. In the adults, cavitation was frequently associated with chronic tuberculous lesions of the intestine and in five instances of the larynx or trachea.

In 40 cases listed by Pagel and Henke the pulmonary lesions are described only as "ulcerative" or "productive". A brief interpretation of these terms is necessary. Under "ulcerative" they include tuberculous lesions characterized by necrosis, ulceration and frequently leading to cavitation. "Exudative" lesions such as tuberculous pneumonia which may resolve or go on to necrosis, ulceration or cavitation are also included. By "productive" is meant the lesions best typified by miliary tuberculosis. The lesions consist of a multiplication of cells, the formation of tubercles usually widespread but not necessarily so. Forty-three out of 50 cases are listed as "ulcerative". Doubtless many of these had cavitation.

c) Caseation. Diabetic tuberculosis has often been described as characterized by large rapidly extending areas of caseation. The term is applied to a form of coagulation necrosis characteristic of non-diabetic tuberculosis as well in which the dead tissue has an appearance quite similar to that of cheese. Just as cheese is a mixture of coagulated protein and finely divided fat, in caseation there is a coagulation of tissue proteins associated with the deposition of considerable quantities of fat. Again we are reminded of the disordered fat metabolism of the diabetic. The protein material is almost solely coagulated protein, which in its elementary composition is related to the simple proteins or to fibrin. Possibly the tubercle bacillus produces substances coagulating proteins. Auclair (quoted by Wells and Long) claims that the fatty substance that can be extracted from tubercle bacilli by chloroform is the cause of the caseation. The phosphatide fraction of the lipoids studied was particularly potent in producing giant cells of the Langhans type. However, Wells and Long[7] conclude that studies so far fail to show that materials extractable from the tubercle bacillus tend to produce the typical massive caseation necrosis. One cannot escape wondering whether the well-known diabetic tendency to fatty degenerative changes in the arteries and liver also favors caseation. No chemical studies are available. In the 55 detailed autopsies of this series, caseating processes are mentioned in 32. However, the incidence of caseation is probably much higher, especially if the term "ulcerative" be assumed to include caseation. In fact, probably a fairer idea of the frequency of caseation is obtained by considering only the autopsies of the Deaconess Hospital. If only the 10 cases with an active process be included, caseation was present in 7 or 70 per cent.

The caseation noted in the above-mentioned 32 cases may be summarized as follows:

Glands alone	1
Glands with other processes	5
Small caseous pulmonary foci only	8
Caseous pneumonia	10
Caseous foci with cavities	8

In the seven Deaconess Hospital cases with advanced processes, the apices were involved by caseating processes in each case. Cavities were present in either or both upper lobes in six cases. In Case No. 7041, boy, 14 years, cavities were found in all five lobes. In Case No. 1977, female, 81.2 years, although caseous nodules were present in both apices there were no cavities. In Cases Nos. 6791 and 6809 cavities occurred in the right lower lobes as well as the right upper. The distribution suggests that apical and subapical caseous lesions with or without secondary infection resulted in cavitation and a bronchiogenic spread to lower portions of the lungs.

d) "Non-sensitized" tuberculosis resembling the overwhelming primary tuberculosis of the

child has been considered characteristic of adult diabetic tuberculosis. It is worth noting that Opie[8], in studying the tuberculosis of Negroes, found that although the usual forms occurred in many cases, in over one-half the autopsies, characteristic lesions of a first infection appeared. Thus, these lesions did not arise at the apex, massive enlargement of the tracheobronchial glands with caseation occurred and there was no evidence of healing or healed scars in berculosis was rarely recognized in a diabetic until an advanced or even terminal stage had been reached.

f) The apices were involved in all the Deaconess Hospital cases. In five of Lundberg's[55] 14 cases, cavities were found in the upper lobes.

g) Miliary tuberculosis occurred in seven cases. This type is so characteristic that it is safe to assume that this represents its incidence in the entire series of 126 cases. (See table 3.)

TABLE 3

SEVEN DIABETIC AUTOPSIES WITH MILIARY TUBERCULOSIS

Author	No.	Age	Sex	Sites of Lesions
Pagel and Henke	1	26	M	Slight tuberculosis right kidney, miliary in bone marrow.
Pagel and Henke	18	23	M	Extensive cavities in lungs, caseous peribronchial areas and miliary lesions, larynx, intestine, liver, spleen and kidneys.
Montgomery	1	51	M	Lungs and spleen; also bronchopneumonia.
Montgomery	3	21	M	Lungs, pleurisy, bronchial and mesenteric glands.
Warren	9	58	M	Fibroid, and "early miliary" in lungs.
N. E. D. H.	7041	14	M	Chronic in lungs with many cavities. Miliary in kidney, spleen, liver, peritoneum.
N. E. D. H.	6809	33	M	Chronic in lungs with terminal miliary lesions in lungs.

the lungs or lymph nodes. Caseous pneumonia and caseation of the tracheobronchial glands were especially noted. If the detailed protocols of the seven Deaconess Hospital cases with advanced processes be consulted, four cases will be found with caseating bronchial or abdominal glands.

a) Case No. 7041, aged 14.7 years, numerous cavities in both lungs with intestinal and peritoneal tuberculosis.

b) Case No. 6791, aged 41.5 years, cavities in right upper and lower lobes, with caseous hilum and mediastinal glands.

c) Case No. 1977, aged 80 years, apical tuberculosis with caseous glands in celiac region.

d) Case No. 11471, aged 48 years, old right apical cavity with rupture into bronchus, caseous bronchial nodes. An old calcified primary focus near the pleura.

All these cases had apical lesions with terminal extensive disseminated tuberculosis. The unusual feature is the occurrence of caseating glands. This similarity of the lesions in diabetics and Negroes is of interest when it is remembered that the tuberculous mortality rates for Negroes is 3.2 times greater than for whites in the United States.

e) Pneumonia occurred in nine of the 55 cases. In most instances caseous pneumonia was associated with cavitation in another lobe. As early as 1884, Dreschfeld[9] reported acute tuberculous bronchopneumonia, running a more rapid course than ordinary phthisis and causing early cavity formation in diabetics. This conception of diabetic tuberculosis has been greatly overemphasized because in the past tu-

Miliary tuberculosis was clearly but a terminal event in a chronic, advanced process in the two Deaconess Hospital cases, in Warren's case and in Pagel and Henke's Case 18. In Pagel and Henke's Case 1, the lesions were not the cause of death. Montgomery's two cases remain the only ones in which it is possible to suppose that a miliary process developed with special rapidity because of the presence of diabetes. Two other instances without autopsy examination occurred among the Deaconess Hospital patients. Case No. 4045, physician, aged 60 years at onset of diabetes, had pleurisy with effusion, developed acute miliary tuberculosis six months later and died at the age of 61 years. Case No. 2687, female, aged 24 years at onset of diabetes, had coma repeatedly, developed acute miliary tuberculosis with pneumonic symptoms and a positive sputum and died at the age of 30 years.

5) EXTRAPULMONARY TUBERCULOUS LESIONS. (Clinical reports chiefly.)

Pleurisy appears in all its forms in diabetes. At autopsy, pleural adhesions were found in all cases with pulmonary tuberculosis. Pleural effusion was present in Case No. 3686, male, aged 67 years, and Case No. 3898. Ritter's[10] case had double pleural effusion. Pneumothorax appeared in one of Ritter's cases and in at least three cases at the Deaconess Hospital. McCormick[11] and Montgomery[4] each noted one case of effusion. Case No. 4743, aged 15 at onset of diabetes in 1923, developed tuberculosis with pyothorax and bronchial fistula in 1931.

Larynx and Intestine. The larynx was involved in but three instances in the series in ta-

ble 1. However, the larynx was not examined postmortem in the Deaconess Hospital series, and probably not in most of the other cases.

Case Nos. 3817 and 3995 in the Deaconess Hospital series had laryngeal tuberculosis. Montgomery noted a patient with laryngeal involvement attending the Phipps Institute Dispensary. In Rubin's[12] group of 526 fatal cases (non-diabetic) from the Montefiore Home, New York City, 90 per cent of those cases complicated by laryngeal tuberculosis had tuberculous ulcers of the intestines. Nearly 50 per cent had other tuberculous lesions in addition to those in lungs, larynx and intestine. By contrast the co-existence of other foci of tuberculosis with pulmonary disease in diabetics is less frequently reported. Rubin remarks that tuberculosis of the intestine is more common in the caseating type of tuberculosis than in the chronic. In fact he states that among 604 patients including 42 diabetics with pulmonary tuberculosis that the laryngeal-intestinal complication was less frequent in the diabetics of similar age than non-diabetics. Tuberculous ulcers in the intestine were found twice in 92 autopsies on diabetics reported by Seegen, the lungs being tuberculous in 40 cases. By contrast Brown and Sampson[13] also report that 50 to 80 per cent of patients dying with tuberculosis have intestinal lesions.

Oberle's[14] diabetic case had tuberculous ulcers of the cecum, larynx and palate as well as pulmonary lesions. Case Nos. 3358, male, aged 44 at death, 5966, female, aged 37 at death and 6809, male, aged 33 at death among the Deaconess Hospital cases had intestinal tuberculosis. The contrast between diabetic and non-diabetic is brought out by comparison with figures of Ophuls. In the first place nearly 10 per cent of all his cases of active tuberculosis were intestinal. Active intestinal tuberculosis without active pulmonary tuberculosis is practically unknown in the literature of diabetes.

Meninges and Brain. Among 126 cases in table 1, not a single case of tuberculosis of the brain or meninges is present. Isolated cases are found in the literature, as Rokitansky's case of meningeal tuberculosis cited by Seegen[15], De Jonge's[16] case of tuberculous involvement of the medulla oblongata, Ritter's case of meningitis, and Drummond's[17] report of a solitary tubercle of the brain in a seven-year-old child with Jacksonian epilepsy. The total number of autopsies upon diabetic children with tuberculosis in table 1 is nine, and of these none had meningitis. Steinmeier[18] found tuberculous meningitis in 132 cases out of 7231 non-diabetic autopsies and 10 per cent of all cases of active tuberculosis. In 186 autopsies upon children under 15 years of age, meningitis occurred in 69 or 37 per cent. Ophuls in San Francisco found meningitis in 12 per cent of all his cases of active tuberculosis. In the first decade about one half of all cases of active tuberculosis tend to terminate in active meningitis. Involvement of meninges and brain in the diabetic in comparison seems conspicuously rare.

Liver. In table 1 four cases showed tuberculosis of the liver as part of generalized infection. Seegen reports two cases in 92 autopsies and one case out of 30 in Rokitansky's series.

Spleen. Miliary tuberculosis of the spleen has been reported by Bagou[19]. A questionable diagnosis of tuberculosis in the spleen was made on one of Montgomery's cases and in table 1 the spleen was involved in three instances.

Kidneys. Naunyn had 2 cases. Williamson had one in 20 autopsies and Seegen reports one case out of 92. In table 1 are found five cases. Again the infrequency of renal tuberculosis in diabetes stands out in contrast to the non-diabetic.

Adrenals. Montgomery described one case in a diabetic and Ogle[20] found a case so considered by Naunyn. Case No. 5434 a physician, aged 38 years, died of Addison's disease.

The Peritoneum. Four cases of peritonitis are found in table 1. Case No. 4296, aged 26 at onset of diabetes, developed tuberculous peritonitis at the age of 34 years. Ascites was extreme during her observation in the Deaconess Hospital in May, 1932, but in October, 1932 her husband, a physician, stated that she had improved.

Lymph Nodes. The records of tuberculous adenitis in diabetes are especially unsatisfactory. In table 1 tracheobronchial glands were involved in 11 instances and the mesenteric glands in 10, but undoubtedly the records are incomplete. In the nine Deaconess Hospital autopsies presenting active lesions, caseous tracheobronchial glands were present in two and caseous mesenteric glands in two. The incidence of tuberculous adenitis in diabetes is better shown by the frequency of calcified tracheobronchial glands demonstrable in a large series by x-ray. In 1659 cases (see Chap. I, *New Eng. J. Med.* 210:8 [Jan. 4] 1934) the incidence was 77 per cent. Including the cases with accompanying pulmonary lesions the incidence of healed and active tuberculosis becomes 79 per cent, which is comparable with Ophul's finding of 75 per cent of his entire autopsy series (3000 cases) presenting either active or healed tuberculosis.

Cervical adenitis is not recorded at autopsy.

Other organs. The bones are rarely found tuberculous in diabetes. In table 1 one case had miliary tubercles in the bone marrow. In addition may be mentioned one case of tuberculous spine in the Lakeville Hospital in Massachusetts in a male 50 years of age who had had dia-

betes for 17 years and tuberculosis for one year.

Case No. 1616, male, aged 14, had a chronic swollen finger joint with a tentative diagnosis of tuberculous dactylitis but without pathologic proof. His finger healed. Case Nos. 3040 and 5661 had tuberculides of the skin.

Of Tompkins's[21] 13 cases of combined tuberculosis and diabetes one had tuberculous epididymitis.

6) Non-Tuberculous Pathology

Pancreas. The size and weight of the pancreas are of little significance owing to the varying degrees of fatty infiltration and fibrosis. The average weight for 18 cases in table 1 was 81 grams, the extremes being 30 and 120 grams. In 13 additional cases the size is given as normal and in 8 the pancreas is described as small or atrophic.

Hyalin changes in the islands of Langerhans were mentioned in 12 cases. The youngest case with hyalin islands was 43 years of age. Sclerosis of the islands was described in 12 cases. Interstitial pancreatitis occurred in one. Incidentally, Ackman and Ross[22] describe a diabetic man with pulmonary tuberculosis and multiple pancreatic calculi. Acinar sclerosis was present in 17 cases. Calculi occurred twice and cancer once. Lymphocytic infiltration was present once. In no case was the pancreas involved by tuberculosis. Nine are described as normal. Warren[23] found 69 normal pancreases in 259 diabetic autopsies. In general the pancreas showed only those changes in the islands of Langerhans and the acinar tissue which usually accompany diabetes.

Glycogenic infiltration in the epithelium of the renal tubules was present in two cases. The distribution of glycogen in diabetic tuberculosis is deserving of special study. Pinner[24] found glycogen in experimentally-produced tubercles, localized either in leucocytes or in the epithelioid or giant cells. Livers studded with tubercles seemed to contain less glycogen in their parenchymatous cells than a normal organ, but liver cells bordering on necrotic tubercles contained more glycogen than similar cells further removed from the foci. Pagel and Pagel[25] found the exudate cells in caseous pneumonia free from glycogen, but glycogen was present in the cellular borders of tubercles. In diabetes the distribution of glycogen in skin, liver and muscle varies according to the control of the diabetes and is especially influenced by severe infections. Rabuchin[26] studied experimental tuberculous animals. They showed a tendency to productive and proliferative processes in the pancreas with, finally, sclerosis and atrophy of the islands of Langerhans. The livers also contained little glycogen. Possibly an understanding of glycogen metabolism would supply the key to the problem of how diabetes lowers the resistance of tuberculous infection.

Other Organs. Arteriosclerosis was prominent in the Deaconess Hospital cases, owing partly to their greater age and longer duration of diabetes. However, even the youngest Case No. 7041, aged 14.8, showed atheromatous plaques in the aorta. In nine others arteriosclerosis is mentioned, associated with atrophy of the heart (1 case) cirrhosis of the liver (3 cases), coronary sclerosis and myocarditis (1 case) and myocarditis, nephritis, renal arteriosclerosis and hepatic cirrhosis (1 case). Unfortunately no data with respect to arteriosclerosis are available for most of the cases. The existence of chronic nephritis in five others suggests the presence of arteriosclerosis as well.

Coronary sclerosis with infarction of the heart occurred in six of the 15 Deaconess Hospital cases and gangrene of a foot in three. Case No. 6809 was but 33.4 years of age when he developed gangrene.

Arteriosclerosis and tuberculosis in diabetics both exhibit a marked tendency to calcification. Even in diabetic children, calcification of the arteries of the legs visible by x-ray occurs. Calcium deposition, according to Wells and Long[7], seems to depend rather on physical than chemical attraction, for it tends to occur in hyalin or homogeneous colloidal masses of whatever chemical nature occurring anywhere in the body. Tubercles undergo calcification probably because they present these physical conditions rather than because of any chemical constituents. The large amount of phosphoric acid that might be derived from the disintegrating nuclei of the necrotic tubercle cannot be held responsible, for Wells found that implanted sterile tissues rich in nuclei take up no more calcium than do tissues poor in nuclei. The chemical composition of the calcific deposits in tuberculosis differs not at all from those occurring in other pathological conditions. In the next section is shown the distribution of areas of calcification in the lungs of diabetics as shown by x-ray. Certainly no failure in calcification is suggested as an explanation of the poor resistance of the diabetic to tuberculosis.

7) Causes of Death. In 69 cases for whom the facts are given, tuberculosis was the cause of death in only 35. Coma was responsible for 11 deaths (including here two deaths designated as "diabetes"). Most of these belong in the period before the discovery of insulin. None of the Deaconess Hospital cases died of coma, all autopsies having been performed since the use of insulin.

In 17 cases the tuberculosis was not sufficiently active or advanced to have played much part as a cause of death. In this group the causes of death were diabetes and coma (3), embolism (2), coronary thrombosis (3), meningitis (2),

otitis media and operation (1), pneumonia (1), gangrene of lung (1), cerebral hemorrhage (1), acute ulcerative endocarditis (1), arteriosclerosis (1), adenocarcinoma of pancreas (1).

In six cases active pulmonary tuberculosis was present, but was overshadowed as a cause of death by gangrene of an extremity (1), acute septic processes (2), cirrhosis of the liver (1), nephritis (1) and arteriosclerotic changes.

8) Quiescent and Healed Lesions. In addition to the 17 cases in which relatively inactive tuberculosis was present, Warren's case 10 had a fibroid process which might have persisted for a long period except for the onset of coma. Dorendorf[27] also comments upon the frequency of old fibrotic processes in mild diabetics. In five of the Deaconess Hospital cases (included in the 17) only healed apical lesions were present. The use of roentgenograms is revealing more early cases with the result that clinical healing of tuberculous cavities and pneumonia is being observed. Wessler and Hennell[28] recently reported eight cases of active pulmonary tuberculosis in diabetics with healing of cavities and extensive exudative lesions under observation. Abundant evidence exists that healing may occur and that even moderately advanced processes may remain stationary for long periods in diabetic patients under modern treatment.

9) Comparison with Tuberculous Lesions in Non-Diabetic. Postmortem examination of diabetic patients reveals no single type or stage of tuberculosis. Small healed foci, small caseous areas in either the lungs or lymphatic glands, more extensive healed or fibrotic areas in the apices are not infrequent. Where death is due to tuberculosis the involvement is frequently extensive with cavitation and terminal pneumonia or miliary spread and often presenting in the background the characteristics of a chronic infection. Comparison with non-diabetic tuberculosis may be made with respect to the primary infection, the type of progression, the types of lesions found and character of reaction to tuberculous infection.

a) *Primary tubercle.* No evidence exists that the primary tubercle differs anatomically in the diabetic from its form in the non-diabetic. It may heal by resolution leaving no trace, or by fibrosis and calcification or ossification. Such areas of calcification in the parenchyma are frequently observed in diabetes. They may be single or multiple and are observed in any lobe, most frequently out toward the periphery. (See Chap. III, *New Eng. J. Med.* 210: [Jan. 18] 1934.) In fact, such areas of calcification were found in 76 out of 87 roentgenograms in diabetics at the Deaconess Hospital.

b) *Cervical Lymph Nodes.* Granting that a simple method of mass infection is one from hand to mouth, the establishment of primary foci in the deep cervical lymph nodes may be expected. No autopsy data for diabetics have been found. However, Case No. 2448, male, aged 18 at onset of diabetes, had draining tuberculous cervical glands at the age of eight years. The apices were dull to percussion at the age of 18 years. Pulmonary tuberculosis was found at the age of 19.6 years and he died at the age of 24 years with an extensive exudative process. (See Chap. III, *New Eng. J. Med.* 210: [Jan. 18] 1934 for x-ray.) Case No. 10887, aged 33.7 years at onset of diabetes had large calcified cervical glands. In a few cases, that also had pulmonary tuberculosis, calcified cervical glands were noted by x-ray. Tuberculous adenitis was treated surgically in Case No. 2007. Case No. 9975, aged 25 years at onset of diabetes, had tuberculous cervical adenitis in childhood. She went through a normal pregnancy in 1932. Case No. 7432 had tuberculous cervical glands at six years and at 16 years chest films showed suspicious markings. Undoubtedly careful search as emphasized by Grabfield and Miller[29] would reveal many more cases of cervical adenitis and the site of primary infection would thus be placed much more frequently in the appendages of the mouth and nasopharynx.

At this point bovine tuberculosis should be considered since it has been shown to be the cause of from 38 to 61 per cent of the cases of cervical adenitis before the age of 16 years. I have found no reports of bovine tuberculosis in diabetics. Calcified mesenteric glands are frequently demonstrated by x-ray, at operation or at autopsy.

c) *Mesenteric Lymph Nodes.* The lymph nodes in association with the intestinal canal should show evidence of disease where large numbers of tubercle bacilli are entering the body by this pathway. Opie found that the frequency of such lesions varies in different parts of the world, and explained the disparity of the incidence of mesenteric lymph node disease between American and English subjects as due to the well-recognized difference in the frequency of bovine tuberculosis. Opie has also observed that "when healed lesions are present in the mesentery, focal tuberculosis of the lung is seldom found. First infection with tuberculosis may occur by way of the lungs or by way of the gastrointestinal tract and the occurrence of one lesion tends to prevent the other."

Among diabetics at the Deaconess Hospital, calcified mesenteric glands were noted only in Case No. 4284, aged 71.5 years, at death. Case No. 1977, aged 81.2 years had caseous mesenteric nodes, as did Case 7041, aged 14.8 years, but both died with extensive and acute tuberculosis. Clinically tuberculous mesenteric glands have been recognized in Case No. 3271, aged 33 years operated upon for supposed acute appendicitis. Case No. 4763, aged 16 years whose

calcified glands appeared by x-ray and who later developed pulmonary tuberculosis was suspected of appendicitis. Case No. 11222, aged 19, and Case No. 4688, aged 11, were operated upon for attacks of abdominal pain and vomiting.

Caseous mesenteric glands were more frequent at autopsy in the cases from European hospitals. Thus Naunyn's Case 49, and Pagel and Henke's Cases 30, 46, 48, 55, 57, 63, 96 and 100 showed active involvement of the mesenteric glands accompanying active pulmonary processes. There is little evidence to suggest the frequency of primary intestinal tuberculosis in diabetics.

d) *Secondary Tuberculosis. Apical Tuberculosis.* More or less localized areas of induration and atelectasis at one, or, more often both apices, usually accompanied by dense pleural adhesions are frequently found in the lungs of modern city dwellers. In this country the incidence is probably less than in Europe, perhaps about 20 per cent, as suggested by Opie's studies on 74 white adults. At the Deaconess Hospital healed apical lesions were only recorded in six cases. In this same series only 7 cases of extensive tuberculosis and 3 cases with small active foci occurred. Roentgenograms show a much greater incidence of apical scarring, and indeed of active apical tuberculosis accompanying a process elsewhere in the lung. Sosman[31] reported 16 cases of healed apical tuberculosis in 182 diabetic patients studied by x-ray.

Apical tuberculosis may be regarded as caused by endogenous or exogenous reinfection. Accepting the first hypothesis, one must suppose that during caseation or softening of tracheobronchial nodes bacilli escape into efferent channels leading to the thoracic duct, thence to the venous blood and back to the lungs. The proponents of exogenous infection cite observations to indicate the rarity of apical secondary disease before the eighteenth year and argue that if the primary foci have become established at the fifth or sixth year it is logical to assume that metastases to the apices should have occurred earlier[27]. In seven autopsies upon tuberculous diabetics reported by Lundberg[55] cavities in one or both upper lobes with adhesions of the apices and parietal pleura were present in six. Case No. 7041, aged 14.8 years, had cavities in both upper lobes. Case No. 5932, male, aged 17 years showed by roentgenogram extension to the right apex subsequent to a lesion in the left middle lobe. This extension occurred while he was under observation and treatment in a tuberculosis sanitarium. Case No. 7263, female, nurse, aged 28 years developed soft hazy infiltration of the right apex extending from just above to just below the clavicle, two years after a roentgenogram showed calcified tracheobronchial nodes. Furthermore, in 87 roentgenograms of diabetics with pulmonary tuberculosis the subclavicular region was involved in nearly *all*. On the other hand, several factors may tend to prevent the immediate establishment of apical disease according to Baldwin, Petroff and Gardner[32]. Under experimental conditions a freshly acquired primary infection results in such a high degree of sensitiveness that relatively large reinfecting doses administered by inhalation produce only slight permanent disease in the lungs. However, a single small dosage, when repeatedly discharged into a given area of hypersensitive tissue over a prolonged period, will ultimately cause reactions of a very chronic type (Krause[33]). Finally, it should be borne in mind that intercurrent diseases like whooping cough, measles, etc., exert a definite and well-marked influence upon latent foci of pulmonary tuberculosis. It is possible that diabetes and especially acidosis may have such an accelerating effect. Under the irritation of such concurrent diseases, inflammatory reaction and particularly edema in the walls of pulmonary and tracheobronchial lymph-node tubercles may increase their permeability so that tubercle bacilli once more escape from them.

e) *Dissemination.* From any actively softening area, organisms may spread by way of the thoracic duct and the venous blood, or more serious still, by way of the arterial blood to all parts of the lungs or body. Bronchiogenic dissemination occurs when invasion of the walls of a bronchiole leads to ulceration. Tubercle bacilli and caseous tissue elements gain access to the duct system of the lungs and a bronchiogenic dissemination is the result.

f) *Types.* Much importance has been ascribed to the difference between proliferative and exudative types of pulmonary tuberculosis. Diabetic tuberculosis has been described as marked by exudative pneumonic processes. Massive pneumonic infiltrations, such as are found in overwhelming primary infections in childhood have been regarded as typical, especially by Sosman. Undoubtedly both proliferative and exudative types occur in diabetics, sometimes alone and sometimes in combination. So far as the 126 autopsies (table 1) are concerned by far the greater majority of the cases, sufficiently extensive to have caused death, are to be regarded as chronic ulcerative pulmonary tuberculosis with more or less acute terminal conditions. Among 40 cases cited by Pagel and Henke and definitely classified as ulcerative or productive, only seven were of the productive type. As a rule cases of fatal tuberculosis exhibit cavitation in one or both the upper lobes with much sclerotic tissue about it. In the lower lobes are found various manifestations of its spread, proliferative or exudative with their sequelae. Thus cavities are often multiple. Clusters of tubercles and patches of pneumonia may occur. Gelatinous pneumonia as in Case No. 11471 may be extensive. Miliary lesions in one or more lobes may occur as in Case No. 6809 due

to invasion of a branch of the pulmonary artery.

The dictum of Koch that there is "no conformity to rule in tuberculosis" indicates how easily one may be led to make conclusions that certain forms of tuberculosis are peculiar to diabetes on the basis of a few observations which would not be borne out if the course of the disease had been observed in a larger number of cases throughout its various stages.

The rarity of acute, generalized tuberculosis in diabetics such as occurs in childhood is striking. Tuberculosis of the meninges, pericardium, pleura, peritoneum or joint surfaces is uncommon. The comparative infrequency of tuberculosis as a cause of the death in diabetic children has been due to their early death from other causes. Warren gives 21 autopsies upon diabetic children from 1.5 to 16 years of age without a single case of tuberculosis. Page and Warren add six cases from 16 years to 20 years without tuberculosis. The average duration of diabetes was less than one year! By contrast Naunyn's four diabetic children, reports of whom were published in 1906, all had tuberculosis at autopsy. In Ophuls' series of non-diabetics, on the contrary, if we exclude the healed cases, 43 or 11.8 per cent of all children in the first decade and 13, or 17.9 per cent of those in the second decade had tuberculosis.

However, since diabetic children no longer need to die of coma, they may, by living longer, more frequently develop tuberculosis in the future. So far the localization of active tuberculosis in the lungs has been very striking in the diabetic child.

In Ophuls' non-diabetic series there were 237 cases with active tuberculosis in the lymph nodes or nearly 10 per cent. In diabetics, active tuberculosis in the lymph nodes is rare except with extensive pulmonary tuberculosis. In Ophuls' 632 cases of active tuberculosis 16 per cent were non-pulmonary, whereas in this diabetic series only three cases, or two per cent, were non-pulmonary. Bones, joints and tendons were involved in six per cent of Ophuls' series of active tuberculosis, the primary focus in these cases being in the lungs in 70 per cent. Bones, joints and tendons are rarely involved in diabetics.

10) Tuberculosis in the Negro and Diabetic. The susceptibility of the American Negro to tuberculosis of unusual form and frequency has long been noted. Opie's[34] study deals with the epidemiology and pathologic changes. Pinner and Kasper[35] review an extensive literature and report a comparison of postmortem observations in 303 Negroes and 219 white patients dying of tuberculosis. A comparison of their findings with those in diabetics is of interest. Miliary tuberculosis is more frequent in Negroes than in whites at all ages, but especially in early childhood. Miliary forms (excluding the terminal type) are rare among diabetics. Hematogenous metastases, occurring in 84.2 per cent of the Negroes seem no more frequent among diabetics than among non-diabetics. Massive lymph-node caseation and massive exudative lesions in the lungs seem characteristic of Negro tuberculosis and in this respect a certain similarity to tuberculosis in the diabetic appears. Pinner feels that, in the Negro, lack of childhood infection is not the explanation. Infection produces a high state of allergy in the Negro but with little coincidental increase in resistance. The diabetic seems to have had normal resistance, judged by the number of calcified foci remaining from early infection, but in some manner loses his resistance after the onset of diabetes.

B. Etiology (A Review)

1) Bacteriology. Certain features of the biology and bacteriology of the tubercle bacillus have a special bearing upon diabetic tuberculosis. Thus it has repeatedly been stated that tubercle bacilli are less often and with more difficulty demonstrated in the sputum than in non-diabetic tuberculosis. We have not confirmed this finding in the present series. Inheritance plays an important part in the etiology of diabetes and the idea has been advanced that in diabetic families a similar hereditary tendency to tuberculosis exists. The marked tendency to rapidly caseating and acute pneumonic processes repeatedly mentioned in the literature suggests some peculiarity in the diabetic tissue especially suited to the metabolic needs of the organism, or possibly to certain phases of its growth. However, it is easy to emphasize chemical and bacteriologic features at the expense of epidemiologic factors.

a) *Variation in Form of Tubercle Bacillus.* Wells and Long[7] from whose review I quote freely, have summarized the evidence indicating that the bacillary form is but one phase of the life of the tubercle organism.

A life cycle including a stage utterly invisible by any method, a finely granular phase, a coarsely granular phase and finally a mature, stable bacillary form, has been accepted by many workers in the field. Various types of pathologic change have been linked with these different forms. In recent years the granular phase has received as much attention as the filterable or bacillary forms, the granules being credited with reproductive character analogous to that of the nucleus in animal or plant cells. Opponents of the school of polymorphism have claimed that many of the forms described were contaminations, which in many instances may easily have been the case, but the importance of the granule, so much like that occurring in the structure of

the ordinary acid-fast rod, seems generally accepted.

A type of variability not previously suspected in Mycobacterium tuberculosis was discovered by Petroff and his collaborators in applying to the growth of the tubercle bacillus the teaching of Hadley and others on microbic dissociation. Under special conditions they were able to isolate rough forms with a notable variation of virulence with the character of the colony. Differences in chemical composition of the rough forms as well as certain biological differences have been detected.

As yet no series of observations indicating unusual forms of the tubercle bacillus in diabetics have been found. We have not been struck by the variety of the usual acid-fast bacillus in active diabetic tuberculosis. Thus, in our series of 245 cases, 109 had positive sputa. This percentage seems low, but it must be remembered that only 160 were under observation in a hospital at a period when tubercle bacilli might be found. The others developed tuberculosis after being treated for diabetes, or were seen but a single time in consultation. Furthermore among the 160 were a considerable number who remained at the Deaconess Hospital but a few days before transfer to a tuberculosis hospital. The number of positive sputa does not seem extraordinarily low under these conditions. Wassmund[36] reported positive sputa in 70 per cent of 60 tuberculous diabetics. Banyai[37] found positive sputa in 27 out of 31 sanitarium cases. Grillo[56] reported positive sputa in 25 out of 30 cases in New Haven. Apparently when diabetic tuberculosis is active and examinations of the sputa are carefully and frequently made, the usual acid-fast forms are found about as frequently as in non-diabetics.

b) *Cultural and metabolic characteristics of the tubercle bacillus in relation to diabetes.* No other pathogenic organism has been so exhaustively studied by chemists as the tubercle bacillus. The distinguishing feature chemically is the wax substance, although protein, carbohydrate and fatty substances with mineral residues are present. The lipins compose 10 to 40 per cent of their dry weight. The important waxy substance has been shown to be a complex alcohol combined with various fatty acids. Lecithin and cholesterol, both of which lipoid substances frequently are found in excess in the blood of diabetics, have not been demonstrated in the tubercle bacillus.

The bacilli contain several types of polysaccharide. A gum-like polysaccharide isolated from the body of the bacillus (similar to or identical with one obtainable from the culture filtrate), is a highly potent reacting "antigen" with the serum of tuberculous patients or horses immunized to dead tubercle bacilli. It does not itself elicit antibody production. This carbohydrate, or derivatives from it, also appears capable of causing severe depressant symptoms on injection into tuberculous animals. Whether a modification of the tubercle bacillus would be found in bacilli isolated from a diabetic is an interesting speculation.

One-half the weight of the tubercle bacillus is protein in nature. Nucleoproteins have been extracted but none were toxic. A nucleic acid was obtained by Ruppel[38] and this "tuberculinic acid" has been the chief center of interest. No true toxin has been isolated from the tubercle bacillus. The febrile and constitutional reactions in active disease are accounted for on the one hand, by deaths of the bacilli and absorption of the compounds liberated from them and on the other hand, by the products of tissue injury. The reactions to tuberculosis in diabetes often exhibit the same unexpected mildness of degree that are seen with acute infections such as appendicitis. The more cachectic the diabetic, the less he seems to react to tuberculosis.

The production of tubercles is the result primarily of local multiplication of tubercle bacilli. The chemical changes in the body fluids, and to a lesser degree in diabetic tissues, are fairly well known. In order to consider their possible effect in providing a specially suitable environment for the organism we may draw upon the review of the nutritional requirements of that organism by Wells. For this purpose knowledge afforded by controlled artificial culture is necessarily the chief reliance.

Its water relations are distinctive. Although it thrives best in a moist atmosphere, it will not grow when covered by a surface film of water, as, for example, below the surface of a liquid culture medium. Dehydration is a marked feature of diabetic acidosis and indeed of uncontrolled diabetes generally. Not only the skin and tongue but internal tissues, such as the eye and trachea, show the effects of great water loss under these circumstances.

This delicate requirement for a proper water relation is believed to be linked with its respiratory peculiarities. The bacillus is strictly aërobic, thrives best in a high concentration of oxygen, and needs a certain minimum of carbon dioxide, although repressed by higher tensions of this gas. It grows at its best close to neutrality, but nearly at its maximum within the wide range of hydrogen-ion concentration, at least from pH 6.4 on the acid side to pH 7.8 on the alkaline. In diabetic coma the pH has been found as low as 7.03.

Its inorganic ion requirements are simple. Apparently potassium, magnesium and phosphate ions are the only absolute essentials, but it is customary to include sodium, chloride and sulphate ions for maximum growth. Sulphur

does not seem to play the part in the oxidizing mechanism of the tubercle bacillus claimed for it in animal cell. Calcium appears quite unnecessary. Iron in minute quantities stimulates, and in larger amount depresses growth.

It obtains its nitrogen from the amino group. Its own proteolytic enzymes are weak; so it does not grow well on whole protein. Ammonium salts, amino acid amides are entirely sufficient, and must be present before much attack can be made on the higher molecular combinations of nitrogen. The protein metabolism is often seriously disturbed in diabetes. Thus during periods of active diabetes, great losses of weight occur with wasting of the muscles. Especially during acidosis and coma, excessive destruction of protein occurs. Occasionally nitrogen excretion of 25 to 30 grams in 24 hours without acidosis occurs, although this is not true of the diabetic under modern control. During acidosis, values of 30 to 35 grams have often been reported according to Joslin. An Italian, described by Joslin, voided at the outset of treatment 7000 cc. urine in 24 hours, containing 48.3 grams of nitrogen. This represented the tremendous amount of protein consumed by an untreated case. Such protein is not normally metabolized and stored. Its destruction provides large amounts of nitrogen amino acid and ammonia. In acidosis the excretion of ammonia in a diabetic may reach 5 to 6 grams in 24 hours. Furthermore, during acidosis and coma a retention of nitrogen occurs due apparently to renal block. The non-protein nitrogen is elevated as a rule and sometimes a value of 90 to 100 milligrams per 100 cc. is reached for short periods.

Case No. 2448, aged 17.9 years at onset of diabetes, entered the Deaconess Hospital December 1, 1921. The twenty-four hour urine contained 30.8 grams nitrogen and 2.2 grams of acetone as well as 660 grams sugar. Ten months later acidosis with excessive ammonia formation and total urinary nitrogen were observed. Although insulin and dietary treatment reduced acidosis, hyperglycemia, and lipemia as well as converted the negative nitrogen balance into a positive balance, he did not adhere to instructions and repeated attacks of acidosis occurred. Pulmonary tuberculosis developed at the end of two years with death four years later.

Low values for nitrogen excretion occurred during the period of treatment with severe undernutrition and are also noted when sudden inauguration of insulin treatment and a diet of moderate proportions are used.

Glycerol appears to be the only alcohol capable of acting as a sole source of carbon for the tubercle bacillus. As noted above, Proskauer and Beck[39] recorded the inability of other polyhydric alcohols, including glycol, erythritol, dulcitol and mannitol, to replace glycerol. Ethyl alcohol failed to support growth of the true tubercle bacilli, while suitable as sole carbon source for most of the acid-fast saprophytes. Kondo[40] confirmed most of these findings. Glycerol should be unusually abundant in blood and tissue fluids of the diabetic, but I know of no analyses. The diabetic in the past has had a diet rich in fat. The common edible fats are chiefly the glycerol esters of stearic, palmitic and oleic acids. These are split in the intestine into glycerin and fatty acid and absorbed into the blood stream. Their resynthesis and storage as fat or their oxidation occurs in the tissues. Another factor in providing much glycerol in the diabetic is the great loss of weight and destruction of fat tissue within his body either in the early stages of the disease or during acute phases, such as acidosis. At such times an excess of glycerol should be set free. The excess of fat in the blood was formerly much more frequent than now. Insulin and the modern diet of more nearly normal proportions should prevent such abnormalities. If these purely diabetic alterations of metabolism have a predominant influence, a difference in the incidence of tuberculosis before and since the use of insulin should be apparent. Thus prior to 1914 among 18 fatal cases tuberculosis developed after diabetes had existed for an average of 3.4 years. Between 1922 and 1931 among 96 cases tuberculosis developed after diabetes had existed 4.6 years.

Simple carbohydrates may support moderate growth of the bacillus in the absence of glycerol, and in the presence of glycerol they lead to a definite enhancement of growth. Gamble and Herrick[41], using the Folin blood sugar method on dextrose broth in which tubercle bacilli had been cultivated three months, found a utilization of dextrose by all of five strains of bacilli, including human, bovine and avian types, of from 12 to 80 per cent of the original content. Sugar utilization was roughly parallel to the amount of growth. Frouin and Guillaumie[42] found that the utilization of dextrose in glycerol-free sugar media increased with the concentration of sugar. One gram of bacilli used up 2.37 grams of glucose in 0.5 per cent glucose solution and 5.84 grams in 4 per cent solution. Eastwood[43] also studied the favorable influence of glucose upon the growth of tubercle bacilli.

Of all sugars tested, glucose has been found by most observers the most suitable. Results with other carbohydrates do not agree.

Bernheim and Dieupart[44] reported that a study of the employees in a sugar factory showed 150 cases of tuberculosis among 1500 workers. The women were more frequently infected than the men. They regarded mechanical injury of pulmonary tissues by the sharp sugar dust as the important etiologic factor.

The presence and amount of glycogen in tuberculous tissue may be influenced by diabetes and especially by insulin treatment. We know

that glycogen disappears from the skin and liver when diabetes is uncontrolled or during the course of severe infections. Yet a normal amount of glycogen may be maintained in the skin and liver under conditions of good control by means of an adequate diet and insulin dosage.

In general, glycogen is found especially in acute inflammatory conditions where there are numerous leucocytes, although it is also found in the fixed tissue cells. Chronic inflammatory processes usually exhibit very little visible glycogen and this is true of tubercles, according to Wells and Long. Generally little or none is present, yet it has been found in both the leucocytes and epithelioid cells of tubercles, and occasionally even in the giant cells. In guinea-pig tuberculosis it is more abundant, presumably because of the more rapid course, and Gierke found much glycogen visible in the epithelioid cells and in the adjacent connective tissue, which is attributed by Pinner[45] to phagocytosis of polymorphonuclear leucocytes containing glycogen, and possibly to disintegration of tubercle bacilli, which contains 4.1 per cent of their dry weight of glycogen (Warkany). Lubarsch[46] states that it is most abundant in experimental tubercles sixteen to twenty days old, disappearing later. Devaux[47] found glycogen often in the same cells that contained tubercle bacilli. It was never found in the lymphocytes. The largest amounts are in the tissues immediately outside the zone of necrosis, but all cells showing nuclear destruction are free from glycogen. The glycogen is, therefore, found in much the same places as the fat deposits. Very young tubercles, that as yet show no necrosis, are glycogen free, but in acute processes associated with polymorphonuclear infiltration glycogen will be found in these cells.

In general, uncontrolled diabetes is characterized by a disappearance of glycogen from the normal depots in liver, muscles and skin and excessive deposition in abnormal sites such as tubular epithelium of the kidneys and the nuclei of liver cells. Insulin causes a return of glycogen to the normal loci and disappearance from the abnormal sites. Possibly the glycogen of tuberculous tissue is somewhat similarly affected.

The nitrogenous needs are in all probability always easily met. In the diabetic at all times there is a considerable amount of amino nitrogen available either about to be synthesized into body structure, or in the course of wear and tear liberation from actively metabolizing tissues. In acute phases and especially in acidosis the tissues must be flooded with nitrogenous compounds easily available for the nutrition of the bacilli. It is not difficult to imagine a frequent oversupply of these life-sustaining substances for the growth of the bacillus.

The carbon requirement is not a simple problem. Glycerol and glucose are both present in the body, but chiefly in the combined state as fat or polysaccharide respectively, both non-utilizable by the bacillus. A certain amount and at certain periods an abnormally large amount of each, however, is free and readily available. It is difficult to determine how much glycerol is present, Long has made rough approximations, and feels that in the blood of non-diabetics at least, it never reaches 0.5 per cent, which is the minimum amount compatible with existence in vitro. The usual amount added in culture media is 5 per cent. As a matter of fact, 8 or 10 per cent affords more luxuriant growth. Long[48] is inclined to believe that the patient's disordered fat metabolism, through an increased available amount of glycerol, may be of more significance than hyperglycemia. The same is a possibility in the confirmed alcoholic, also of notorious susceptibility to tuberculosis, in whom the alcohol is metabolized in place of a normal diet.

c) *Virulence.* By virulence is meant the power of the tubercle bacilli to produce progressive tuberculous disease. Human types of low virulence have been isolated, particularly from cases of lupus. It might be supposed that the apparent severity and rapid progress of diabetic tuberculosis were due to chance infection of this relatively small group as compared with tuberculous patients as a whole, by organisms of uniformly high virulence, whereas in the larger group many cases were infected with organisms of attenuated virulence. No evidence whatever may be adduced in support of the hypothesis. In fact it seems unreasonable in view of the fact that in so large a percentage of diabetic cases, definite familial exposure is known and therefore presumably the same organism infected both diabetic and non-diabetic members of the family.

Long[48] points out that virulence may be related to the initial capacity of the organisms to grow in cells. He cites the experiments of Maximow who noted that tubercle bacilli tended to die out after growing in cells while non-pathogenic acid-fast bacilli did not. Perhaps the phagocytes of Metchnikoff and the later "macrophages" are really cells providing good condition for growth. Again we are led back to the thought that it is the cells of the diabetic which in some way provide advantageous cultural conditions for the tubercle bacilli.

2) Immunity of the Diabetic. Growth of the bacilli in human tissues clearly depends upon chemical factors such as availability of substances for nutrition, the reaction and oxygen tension of environment, water relations, temperature, etc. Many other conditions, as yet hardly studied, may apply. In addition to a favorable effect upon growth, the diabetic environment might bring about a relative increase in virulence by favoring a dissociation of organism (according to the work of Petroff and as-

sociates) leading to the predominance of a virulent form. Long believes that the explanation of native immunity lies in these factors.

Native immunity must vary greatly in different individuals. The variation in size and extent of old healed lesions of tuberculosis at autopsy is difficult to explain on the basis of accidents in the virulence and dosage of original infection. The native immunity of diabetics as a group is not low if one considers the following facts

a) Deaths from tuberculosis in diabetic children are rare. (See Chap. III, *New Eng. J. Med.* 210: [Jan. 18] 1934.)
b) The ages at death of tuberculous diabetics are not less than among non-diabetics.
c) The evidence of healing shown by calcified glands in 1659 diabetics routinely x-rayed shows that 77 per cent have been infected and have partially healed.

It is obvious that native immunity does not prevent the growth of bacilli in the tissues. Even though the first infection is healed, controlled or arrested for many years, re-infection from without or a change in the host which causes a relighting of an old focus leads to tuberculous disease. A new factor is now present. Necrosis of tissue is a characteristic feature, largely due to the hypersensitive (or allergic) state of the tissues to products of the bacillus which were formerly relatively harmless. At autopsy tuberculous patients are practically never seen in whom the pathologic changes have been uninfluenced by hypersensitiveness. On the contrary, it is the hypersensitive state which makes the tuberculosis fulminant. Indeed most caseation and necrosis occur because of hypersensitivity. Although some immunity is acquired from primary and even repeated infections, it is not persistent or effective in the face of massive re-infection and its chief effect is to alter the character of the resulting process by tending to prevent widely disseminated lesions. Does diabetes affect the immunity conferred by infection? Does it affect the degree of hypersensitiveness? We have seen that the tissues of the diabetic may well provide a medium richer in such nutrients as glycerol, amino acid nitrogen and glucose and so encourage multiplication of bacilli. Pathologically chronic processes of caseation and extensive cavitation largely localized in the lungs are most commonly the cause of death indicating definitely sensitized tissues with sufficient immunity to avoid frequent generalized processes. Clinically the symptomless character of many cases has been greatly stressed which would suggest a lesser degree of hypersensitiveness than in non-diabetic tuberculosis. However, this point has been grossly exaggerated and will be discussed later. An insidious onset with frequent "colds" is common in non-diabetics. Early diagnosis of tuberculosis in diabetics has been rare in the past, probably because too often the attention has been centered on diabetic treatment. If one could be convinced that improvement in diabetes was regularly correlated with improvement and healing in the tuberculosis, it would clearly indicate the importance of certain metabolic changes in the host. Tuberculosis sometimes develops even when diabetes is well controlled and contact with active cases excluded. Case No. 1977, aged 80 years, although confined to her room in a hospital and under constant diabetic treatment for two years, died of pulmonary tuberculosis and tuberculous peritonitis. She had no fever, no cough, and no physical signs were recognized until her terminal illness which was regarded as pneumonia. It must be admitted that whenever improvement has occurred in our experience, not only good diabetic treatment but good treatment of the tuberculosis has been necessary. However, most observers have agreed that control of the diabetes does have a definitely favorable effect. The converse is clearly shown by the incidence of tuberculosis in patients who have had coma. Recently two girls, ages 19 and 24 years, after making unusually good progress in a sanatorium, broke down a year later when diabetic treatment was neglected. This again supports the idea that improvement and healing in diabetic tuberculosis are due not only to rest, and removal from an environment favoring re-infection, but also in considerable degree to a better metabolism of the host, probably affecting intracellular nutritive conditions of the bacilli.

3) Allergy and Resistance. All students have agreed that primary infection confers some immunity against re-infection but this immunity is temporary and fleeting. Zinsser[49] considers that it acts rather to modify the effects of re-infection than to prevent added bacilli from having any effect. It sets up a reaction between body and organism tending to chronic and limited tuberculous formations rather than to disseminated and progressive foci. Therefore, in studying diabetics it is of primary importance to determine whether tuberculosis tends to such chronic and limited types if we seek to understand the effect of diabetes upon the development of immunity.

The persistence and completeness of immunity depend entirely upon the size of the reinfecting dose and the virulence of the organism. In the children of tuberculous parents, repeated and almost constant new infections may occur. The effects will vary in different persons according to the dosage, the virulence of the organisms and the immunity or resistance of the individuals. Furthermore, the resistance

or immunity of the individual may vary from time to time in relation to his general health, the development of complications, etc. In tuberculosis the reticulo-endothelial cells seem to play more than one defensive rôle. As phagocytes they are of chief importance, most of the tubercle bacilli, after a brief sojourn in the polymorphonuclear leucocytes, being found inside reticulo-endothelial cells. Next, they are the chief cells that form the encapsulating tissue to limit the spread of the infection; and also, it is to be presumed that they act as prime factors in the immunological defense against the tubercle bacilli as they seem to be against other pathogenic bacteria. In addition to this they seem to play a formerly unsuspected rôle in chemotherapy, for it has been found that if the amount of available reticulo-endothelium is reduced by splenectomy or by blockade, the efficiency of chemotherapeutic agents is correspondingly reduced. This may possibly be because the chemotherapeutic agent acts mainly by stimulating the reticulo-endothelial cells, or because these cells transform the drug into a more potent form. It is to be noted that most of the chemotherapeutic agents that have seemed to accomplish some increased resistance to tuberculosis, have been substances that are taken up by the reticulo-endothelium. In diabetes these cells are sometimes found to be distended with fat, especially under conditions when the diabetes is relatively uncontrolled. In cases reported by Warren and Root[50] lipoid material was deposited chiefly in the reticulum cells of the spleen, the Kupffer cells of the liver and endothelial cells of lymph nodes. However, none of these cases died of tuberculosis. When the fat of the blood is increased in coma, the function of these cells is reduced and resistance to tuberculosis diminished. Experimentally, interference with this system according to Gay[51] may facilitate infection in the normal animal, if the system has been thrown out of function, or, on the other hand, infection is prevented if the macrophages are stimulated to greater activity.

That diabetes probably does not increase the degree of sensitivity, but rather diminishes the allergic state is suggested by the rarity of acute exudative lesions in the serous membranes and especially the joints of diabetics. Indeed, Labbé believed that in diabetic acidosis, allergy was in abeyance and that then the resistance to re-infection associated with the allergic state similarly was lowered. Beckman[52] also suggests that acidosis may suppress the usual allergic response to reinfection and thus explains the relatively slight symptoms produced by tuberculosis in the diabetic. Certainly it appears true that diabetic coma and uncontrolled diabetes have been frequently followed by a flare-up of tuberculosis in our cases.

The chronicity of some cases of pulmonary tuberculosis even in young diabetics is surprising. Case No. 2274, boy, lived with his tuberculous grandfather till his death when the boy was six years old. He developed diabetes at the age of six years and tuberculosis was recognized at the age of 11 years. At the age of 16 years both lungs are extensively involved (see Chap. III, *New Eng. J. Med.* 210: [Jan. 18] 1934) but he has grown normally and weighed 93 pounds in December, 1932. Case No. 10163, female, developed pulmonary tuberculosis at the age of 14 years and spent four years in a State Hospital. Sputum was positive. She developed diabetes at 28 years. In July, 1932, at the age of 35 years, she was able to do her housework, weight 119 pounds. Pulmonary involvement is extensive. (See Chap. IV, *New Eng. J. Med.* 210: [Jan. 25] 1934 for roentgenograms.)

4) Contagion of Tuberculosis. Among the 245 cases of this series definite infections within the family in contact with the patient are recorded in 65. In 40 others, family infection is possible but not definite, in that no reliable data are available as to the presence of a positive sputum, the frequency or duration of contact. In the children exposure to tuberculosis occurred in the family or at work as in Case No. 5932, who worked in a grocery store where another employee was found to have a positive sputum. Such exposure was found in all but four cases for whom we have been unable to get the data. Fitz[5] reported 11 cases (31 per cent) with tuberculosis in the family and two cases (6 per cent) with both diabetes and tuberculosis in the family.

The hereditary tendency to diabetes is definite. Is there hereditary infection with tuberculosis? Recently Calmette[53] has reported the cultivation of a tuberculous ultravirus obtained from the lymph glands of infants born of tuberculous mothers and dying of an intoxication within a short period after birth. Deaths from tuberculosis in diabetic children are almost unknown. The incidence of known maternal tuberculosis in diabetic cases is too small to support this interpretation of the mode of infection.

Next to familial contact in importance is the prevalence of tuberculosis in the community. Variations from decade to decade are considerable. Differences between European and American communities, and between rural and urban communities are also great. Zachs[54] reported that in the families of the 110 children with adult tuberculosis, tuberculosis was known to exist in 69 or 64.4 per cent. In our twelve diabetic children, family exposure is known in seven or 58 per cent. Although the number is small, the comparison suggests that contact with active cases rather than the influence of diabetes should be stressed. Not only the family but the danger of unpasteurized milk fortunately now

much diminished, the occasional case of open tuberculosis in school teachers emphasized by Klein and rare carriers of bacilli without evident lesions such as the cases described by Floyd and Novack must not be forgotten in trying to trace the infection in diabetic children.

Summary

1) One hundred and twenty-six autopsies upon tuberculous diabetics are summarized.

2) The tuberculous diabetic need not proceed rapidly to death from tuberculosis. At autopsy healed and healing lesions are frequent.

3) Primary foci occur in childhood and areas of calcification in the parenchyma were observed in 76 out of 87 chest films of adult tuberculous cases.

4) Miliary, meningitic and acute generalized tuberculosis are rare.

5) Caseation and cavitation involve chiefly the upper lobes although the first lesions of reinfection were sometimes observed at or below the level of the hilum.

6) Acute pneumonic or miliary processes were found usually as terminal events in a chronic pulmonary process.

7) The presence of large caseating lymphatic glands together with pulmonary tuberculosis in five cases resembled the tuberculosis of Negroes.

8) Because of primary infection early in life, diabetics are highly sensitized. Their resistance seems to have been normal until diabetes developed.

9) Etiologic factors introduced by diabetes are concerned chiefly with changes in body chemistry which may favor multiplication of bacilli or development of variants. These include disordered protein and fat metabolism with increased amino acid nitrogen and glycerol in the tissues, induced especially in periods of acidosis.

10) Contact with open cases is known in a sufficient number to make evaluation of other factors difficult.

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ARTERIOSCLEROSIS IN THE ARTHRITIC*

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THE presence of arteriosclerotic changes in arthritis has been very noticeable during the work done in the Survey of Chronic Disease at the Robert B. Brigham Hospital. The frequency of vascular changes in the radiology reports directed attention to the probable value of a study of such changes. All of the radiograms taken on 251 arthritics were examined from the point of view of blood vessel changes.† Where there was definite sclerosis it was noted as a positive observation in that patient, irrespective of its location. Some showed sclerosis only in the pelvic vessels; some only in the extremities.

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†Nissen—Spencer—For records and addresses of authors see "This Week's Issue," page 109.

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(The location of sclerosis has not been emphasized in this paper because its etiology is unknown.) Although in a number of the radiograms sclerosis of veins as well as arteries was obvious, we have dealt only with arterial changes. The changes noted in the arteries were considered under five headings,—negative vessels (no vessels seen), barely visible vessels, questionable (which means probable) sclerosis, definite sclerosis and marked sclerosis. The group analyzed in this paper,—251 arthritics—was dealt with as in a recent paper by the authors on Sugar Tolerance in the Arthritic. The patients were studied primarily from the point of view of abnormality of blood vessels. Subdivisions were made and other systemic involvements were also considered. The longer one studies a group of arthritics clinically over years, the more fascinating the unsolved riddle as to the etiology of arthritis becomes. The authors' studies suggest more and more that the answer to the riddle must lie in that group of arthritics whose condition baffles the physician and for the patient spells years of helpless crippling.

The Survey has shown the value of long clinical observation of a large group of chronic patients, a number of whom have been seen, followed and examined regularly by members of the Staff for fifteen years and more. It is hoped that facts obtained from this composite clinical picture of arthritis may stimulate interest in other researchers whose laboratory facilities are more extensive than ours, so that exhaustive investigation by group coöperation into the more technical problems suggested by the clinical findings may eventually solve the riddle where individualistic activity has heretofore failed.

The 251 patients studied were divided as follows:

Sex		*Age*		*Duration*		*Type Arthritis*	
Male	(108) 43%	1-20 yr.	(22) 9%	Months	(46) 18%	Type 1	(90) 35%
Female	(143) 57%	21-30 "	(42) 17%	1 yr.	(26) 11%	Type 2	(72) 29%
		31-40 "	(59) 23%	2 yrs.	(24) 11%	Mixed Type	(37) 15%
		41-50 "	(51) 20%	3 "	(18) 8%	Struempell-Marie	(18) 7%
		51-60 "	(50) 20%	4 "	(11) 4%	Rheumatic Fever Syndrome	(9) 4%
		61-70 " and over	(27) 11%	5 "	(23) 9%	Still's	(15) 6%
				6-10 yrs.	(57) 22%	G. C.	(8) 3%
				11-20 "	(38) 15%	T. B.	(2) 1%
				Over 20 yrs.	(8) 3%		

Definite Tissue Alteration	(103)	40%	*Elevated Blood Pressure*	(26) 14%
Weight loss	(81)	31%	*Fever*	(83) 33%
Weight gain	(22)	9%		
Urinary Abnormality			*Activity of Arthritis*	(97) 39%
Sugar	(26)	10%	?? *Activity Arthritis*	(37) 15%
Nephropathies	(65)	26%		(134) 54%
Foci Infection			*Clinical Heart Abnormality*	(62) 25%
Tonsils	(133)	54%		
Teeth	(45)	18%		
Antra	(14)	6%		
G. I. tract	(14)	6%		

Blood Vessel Changes by Radiographic Examination

Negative Vessels (no vessels seen)	(51)	20%
Barely Visible Vessels	(59)	25%
Questionable (probable) sclerosis	(34)	14%
Definite sclerosis	(89)	36%
Marked sclerosis	(18)	7%

One hundred and forty-one patients, or 57 per cent of the 251 arthritics, at different ages, showed probable, definite or marked sclerosis. One hundred and twenty-three patients were in the first four decades of life; 128 were over forty. Of the latter group, 72 per cent showed sclerosis. This is what one would expect to find; but one does not expect to find in a group of 123 *under* forty years of age, forty-eight, or 38 per cent, who show probable to definite sclerosis. Fifteen of these, or 12 per cent, showed probable sclerosis; 31, or 25 per cent, definite sclerosis; and 2, or 1 per cent, marked sclerosis. As soon as these figures were tabulated it became obvious that here was material for further investigation; for certainly it is unusual to find 19 per cent of a group of 251 patients, irrespective of the type of arthritis, showing probable or definite sclerosis before the age of forty. If the 15 whose sclerosis might be questioned are omitted it is still significant that 33, or 26 per cent of a group of 123 showed arteriosclerosis under the age of forty; and it is even more vital a fact that 12 of the 33 were under thirty years of age. Eighteen of the 48 patients showed no measurable joint change and were able to carry on fairly normal functional activity. Ten of the 48 were ambulatory and able to get about with some joint hand-

icap. Twenty of the 48 showed multiple and marked crippling and deformity. It is interesting to speculate on what the future years hold in store for the first two groups, that is the ambulatory with slight joint handicap and the ones with no handicap, but who do show sclerosis. Will they join the 20 who already show marked impairment of functional activity, or will they not? It raises the question: Does early sclerotic change have prognostic value for the arthritic?

SERIAL RADIOGRAPHIC STUDY

Serial radiograms were available in many instances, and it was possible to trace the changes in blood vessels in 41 patients from negative in the beginning to sclerosis. This certainly emphasizes the value in patients with chronic disease of regular serial radiographic studies of parts of the body other than those which are the outstanding chief complaint. If every aid is used to obtain various body measurements year after year (lack of funds is usually the reason that this policy is not generally pursued) sufficient scientific data should be accumulated from the group so followed that more rapid progress toward the solution of certain phases of chronic disease may result. This serial radiographic study raises the question as to whether it is normal to visualize blood vessels by radiogram, or is such visualization a forerunner of sclerosis, and has it diagnostic value? It is a known fact that postmortem examinations show diffuse or isolated areas of arteriosclerosis. It is also a fact that the development of sclerosis is much more rapid in some people than in others. It is not a deterrent to functional activity in some, while in others apparently it is the chief cause of mental or physical disability. The unusual point brought out here is the age of the patient at the time of the appearance of sclerosis and the observation of its progressive development. During the years in which sclerosis appeared in these patients followed by serial radiograms, in the younger group the proportion of those who were physically active and those inactive is roughly equal. In the older group, 80 per cent were active physically; 20 per cent inactive. The following is a chart presenting the ages of patients during which the vascular changes occurred. It is interesting to note that a number of these patients had a low sugar tolerance.* However our study has not proved any consistent definite association between arteriosclerotic changes and low sugar tolerance.

No constant standard technique was used in the radiograms studied in this paper. When radiographic technique is standardized the question of visibility of blood vessels being normal or abnormal may be answered. Such standardization is therefore important, particularly for a serial study of sclerotic changes. At the present time, there is no question as to recognition of definite or marked sclerosis, but the earliest detectable form is still debatable.

*Sugar Tolerance in the Arthritic. Nissen and Spencer. New Eng. J. Med. 210:13, 1934.

SERIAL RADIOGRAMS OF SOME OF THE ARTHRITICS STUDIED

Patient	Vessel Change: Negative	Visible	Questionable	Definite	Marked	Type Arthritis	Age
Male	X					Mixed	32
				X			34
Male	X					Struempell-	25
			X			Marie	33
Male	X					Struempell-	19
				X		Marie	20
Male		X				Rheum. Fever	16
				X		Syndrome	18
Male	X					Rheum. Fever	27
				X		Syndrome	29
Male			X			G. C.	27
				X		Arthritis	30
Male			X			Rheum. Fever	28
				X		Syndrome	35
Male		X				G. C.	32
				X			33
Male		X				T. B.	27
				X		Arthritis	30
Male	X					Type 1	33
				X			35
Male		X				Type 1	22
				X			27
					X		28
Male		X				Type 1	34
				X			38
Female			X			G. C.	23
				X			26
Female		X				Type 1	24
				X			28
Female		X				Type 1	24
			X				27
Female		X				Type 1	19
			X				21
				X			25
Female		X				Type 1	39
			X				49
				X			50
Male			X			Type 1	38
				X			42
					X		44

INCIDENCE OF SCLEROSIS

There was a slightly higher percentage of sclerosis in males than in females. In Type 1 (90) 38 per cent showed probable, or definite, sclerosis. The appearance of sclerosis was noted in 27 per cent of the 90 when they were under 40 years of age. Type 2, and the Mixed Type, had the highest percentage of sclerotics as one would expect. Of the 72 patients in Type 2, 78 per cent showed sclerosis; and 7 per cent were under forty. In the Mixed group, 73 per

cent of the 37 patients showed sclerosis, and 8 per cent were under 40 years of age. In the 18 Struempell-Marie arthritics, 44 per cent showed sclerosis and 39 per cent of these 18 were under forty. Nine patients were listed as Rheumatic Fever Syndrome, 45 per cent of whom showed sclerosis; and these were all under forty. The 8 gonorrheal arthritics all showed sclerosis; and 88 per cent were under forty. It is unavoidable to be interested in any startling observation, and the fact that this entire group, though a small one, showed sclerosis deserves more study.

TISSUE ALTERATION

Another striking observation which has become more noticeable as the study of arthritis has progressed is the marked variation in tissues, such as weight loss, weight gain, muscle atrophy, obesity, and intermittent gains or losses in weight. This change in the homeostasis of tissue balance appears to be of definite significance, and is also being studied and analyzed in more detail for future publication. It is noted in this paper as marked loss or marked gain in weight at the time the radiograms were taken. To repeat, 81 of the 251 patients studied showed marked loss of weight and 22 marked gain. Males and females showed equal percentage of weight loss, but the females outnumber the males in weight gain six times. The blood vessel changes in the group showing weight loss were as follows:

Negative Vessels (no vessels seen)	(17)	21%
Barely Visible Vessels	(23)	28%
Probable Sclerosis	(11)	14%
Definite Sclerosis	(27)	33%
Marked Sclerosis	(3)	4%

Comparing this table with the similar table of the entire group of arthritics irrespective of anything but vessel change, it is extremely interesting to note that the percentages are almost identical.

Of the 22 showing marked gain in weight, six had visible blood vessels and 16 definite sclerosis. Therefore, with 50 per cent of the group with *loss* of weight and 72 per cent of those with *gain* in weight showing probable or definite sclerosis, it seems suggestive that there is a connection between the mechanism regulating tissue change and vascular change. Is it not probable that variability of tissue (weight gain, loss or constant variation) is of greater importance than heretofore has been considered? Because this is certainly a disturbance of the normal tissue balance of the body. In the group showing gain in weight, 6 showed nephropathies, none sugar, in the urine; 13 had tonsils. Of the group with loss of weight, 24 showed nephropathies; 10 sugar; and 34 had tonsils.

BLOOD PRESSURE

The frequency of elevated blood pressure in arteriosclerosis in the group studied was not constant or marked. Only 36 out of the 251 patients showed high pressure. Five of these showed negative or visible blood vessels; 31 showed probable or definite sclerosis; 17 of the 31 were in the group of early sclerotics under forty. The relationship between elevated blood pressure and arteriosclerosis is not unexpected, because the work already done on essential hypertension without demonstrable proof of sclerosis is well known, as is the presence of marked sclerotic changes in blood vessels without elevation of blood pressure. Since one may find plus or minus blood pressure readings with or without sclerosis in non-arthritics, it is not astonishing that one finds comparable measurements in arthritics.

URINARY ABNORMALITIES

Of the 65 showing nephropathies, 27 had negative or visible vessels; 38 were in the sclerotic group. Seventeen of the 38 were in the group with sclerosis under forty. The incidence of sugar was negligible.

SEVEN FOOT RADIOGRAMS OF THE HEART

Seven foot radiograms of the heart were taken on 61 patients. Fifty-three or 85 per cent showed definite changes in the heart and 37 or 61 per cent showed definite changes in the blood vessels. The cardiac changes consisted of general enlargement of the heart, either of the rheumatic or sclerotic type, and left ventricle rounding. Eighteen or 30 per cent showed denseness, thickening, tortuosity or actual calcium plaques in the arch. The patients' ages ranged from the first to the eighth decade. Thirty-five of the group were under 50; 26 over 50. Though 53 patients showed heart abnormalities by radiogram, only 16 are listed as "Clinical Hearts." Twelve of the 48 patients with sclerosis of the vessels appearing under the age of forty had seven foot radiograms of the heart taken. Two of the 12 showed hypertrophy and sclerotic hearts; 4 showed hypertrophy and rheumatic hearts; 2 showed definite changes in the arch; and only 4 were considered normal hearts. An interesting fact is that in a certain number of these patients the changes in blood vessels and heart antedated the appearance of the symptomatic joint involvement; as the vascular changes were demonstrable by radiogram at a time when the duration of the arthritis was noted as a matter of only months. Again it is well to emphasize as this series indicates that the actual duration of arthritis in itself is not a deciding factor as to the prognosis of the case. Actually, of the 141 patients showing probable and definite sclerosis, 30 gave a his-

tory of duration of arthritis from 6-10 years; 26 a duration of months, with the remainder showing small percentages in the other year-duration groups. Of the 48 early sclerotics, 15 had arthritis of 11-15 years' duration; 15 a duration of months, and 11 with duration of 6-10 years.

FEVER AND ACTIVITY OF ARTHRITIS

Apparently the incidence of sclerosis had little relationship to fever or activity of the arthritis. In fact of those with fever and activity of disease a few more were in the groups with negative or merely visible blood vessels than were in the sclerotic groups.

FOCI OF INFECTION

Tonsils predominated as probable foci of infection. The majority of the 133 with retained tonsils were in the older group of patients. The presence of tonsils may be a source of toxin irritation with intermittent absorption, and in older people particularly may well play a part in the gradual progression of arthritic changes, or even in their production. The purpose of this paper is not to go into detail regarding foci of infection. It is by no means our contention that the mere presence of tonsils, which may or may not have the appearance of chronic inflammatory remissions and relapses, is sufficient, irrespective of age and the patient's physical condition, to indicate their immediate removal in hope of producing a miraculous alleviation of the arthritic syndrome.

Thirteen of the group with tonsils were in the sclerotic group under forty, while 67 were in the group with probable and definite sclerosis *over* forty. This of course indicates that tonsils are more uniformly removed in childhood in the present day than a decade or so ago. The technique of tonsillectomy has also been perfected, lessening the chance of retention of tonsillar remnants.

CONCLUSION

If one studies the material presented in this paper, one is likely to consider the prognostic significance of definite arteriosclerosis in an arthritic group irrespective of type, whose age is under forty. This is an enticing idea, because a large percentage actually did show progressive vascular changes irrespective of the arthritic type. Does this by any chance indicate a disordered mechanism, which in turn is responsible for the joint changes? Or does the variety of the arthritic types represented emphasize again that it is the individual rather than the type that makes for degeneration or change in tissue function in the arthritic? Is the tendency to produce sclerosis merely another manifestation of a catalytical "X" which may be the producer of the arthritic syndrome and may act before the joint subjectively is involved? The proportion of sclerotics under forty years of age in this group of arthritics is much larger than one anticipates or actually finds in comparable groups who have no arthritic manifestations. Are the changes in the vascular system merely another link in the chain comprising the various systemic changes present in arthritis? May the vascular changes prove to be another lead working toward a common etiological centre, which may have to do with the production of arthritis? These questions deserve intelligent consideration.

SUMMARY

1. Reiteration is frequently brevity in its most subtle form. Therefore, once again we note that our study of arthritis is primarily clinical.
2. Two hundred and fifty-one arthritics form the material upon which this paper is based. One hundred and twenty-three were under forty years of age. Forty-eight or 38 per cent of these showed probable, definite or marked sclerosis. The fact that sclerosis was present at such youthful age in a group of this size is significant and worthy of further investigation. Yearly serial x-ray studies of arthritics seem to be indicated in order to note progressive vessel changes as well as changes in heart, gastro-intestinal tract, bone or joints. Otherwise it will be impossible to agree upon what is a normal blood vessel roentgenologically. Unless there is agreement there is little chance of detecting early vascular change indicative of later sclerosis or of discovering treatment directed toward the prevention or arrest of the sclerosing process.
3. The relationship between arteriosclerosis and elevated blood pressure, urinary or clinical heart abnormalities was not remarkable. Fifty-four per cent of the group showed definite or questionable activity of the arthritic syndrome.
4. Possible foci of infection in teeth, ears, antra, gastro-intestinal tract, genito-urinary tract and respiratory tract were present in varying, but not marked, percentages. The presence of tonsils or tonsillar remnants was a more prominent source of probable infection, 54 per cent of the patients showing retained tonsils. Tonsils played a small part, however, in the younger group of sclerotics; only 13 in a group of 48 sclerotics under forty possessed tonsils. On the other hand, 67 of the 93 sclerotics over forty kept their tonsils.
5. Known duration of arthritis seemed to have no definite bearing on the incidence of sclerosis. In some instances changes in the vascular system evidently antedated the onset

of arthritis symptomatically. In others, the arthritis had been present for years before any demonstrable change occurred in the vessels.

6. Seven foot plates of the heart had been taken of 61 of the 251 patients studied. Eighty-seven per cent of these showed definite changes in the heart and aorta. Sixty-one per cent of the group showed blood vessel change and cardiac change. Only sixteen of the fifty-three with radiographic changes in the heart presented recognized clinical signs of cardiac damage.
7. Definite change in the homeostasis of body tissue is again noted in the arthritic. One hundred and one, or forty per cent of the group, showed such imbalance. Seventy-nine, or thirty-one per cent, showed marked loss of weight; twenty-two, or nine per cent, marked gain. The importance of the involvement of multiple body systems in the arthritic is stressed once more, and the problem stated again is this: Is arthritis the cause of, the result of, or merely coincidental with, the changes in the functions of the different body systems?

MEDICAL PROGRESS

PROGRESS IN THE DIAGNOSIS AND TREATMENT OF SYPHILIS, 1931-1932

BY AUSTIN W. CHEEVER, M.D.*

DURING the period covered by this report there has been no spectacular accomplishment, but interest in the problem of syphilis is still intensive as is indicated by the reports of clinicians, research workers, and technicians, who are striving for better control of syphilis by increasing its curability with more effective methods and drugs, and by educating the public and members of the medical profession with the hope of lowering its prevalence.

Cole[1] believes that there would be a tremendous decline in syphilis in the next twenty-five to thirty years if all physicians could be impressed with the necessity of early diagnosis, of thorough treatment, and of prophylaxis; if the laity could be made to realize the consequences of this disease; and if all applicants for marriage could be compelled to undergo a physical examination. In a discussion of the present extent of syphilis, Cole refers to a questionnaire sent out in 1926 by Jadassohn to fifty-one specialists in nineteen countries. The answers show a unanimity of opinion that the disease was declining in fourteen of these countries at that time, attributable to the use of arsphenamine. However, Fuss, who has recently reviewed the matter of incidence in Europe, is quoted[1] as being of the opinion that the disease is increasing again, due either to a periodic fluctuation or to greater promiscuity in connection with unemployment, immigration, and other causes.

In Indo-China[2] the venereal diseases take a place second only to malaria in importance, but there is almost a complete absence of syphilis in New Caledonia and New Hebrides and a similar absence in Fiji, Solomon Islands, and New Guinea. At the Dermatosyphilologic Clinic at Florence[3] it has been found that venereal disease has decreased in the last five-year period over the previous three periods: total syphilis having decreased almost one-half, secondary syphilis having dropped to little more than one-third, with a still greater decrease in venereal ulcer and gonorrhea. During the second half of this five-year period, however, there has been a marked increase so that as the period closes the figures are gaining.

At the St. Louis Hospital, Paris, in 1931[4] there was a decrease in the number of cases and this was attributed to the economic crisis. In the last few months of 1931 when unemployment was at its worst, there were fewer cases of syphilis and soft chancre. At this time the houses of prostitution reported that their clientele had decreased thirty to fifty per cent.

In our own country the report of the Surgeon General of the Army[5] showed in 1930 the lowest admission rate for venereal diseases in the history of the service. These diseases at that time caused about eight per cent of all admissions to hospitals and quarters, and two per cent of the deaths. In the Navy[6] the admission rate in 1930 showed an increase over 1929, but this can probably be accounted for by the visits of the ships to ports in the West Indies. An increase of reported cases in 1931 over 1930 in Massachusetts[7] has been shown.

Granger[8] goes so far as to say that "not a man or woman lives who does not elbow an infected individual every day. It is increasing and its present stronghold is among the Negro race." Syphilis is more common among the colored population than among the white, and the Negroes do not realize its ravages. When there are no manifest symptoms or signs they are extremely lax with their treatment. He

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feels that it is a very serious obstacle, the most important single one, in the Negro health problem, and he pleads for more careful investigation and treatment among the colored.

Recognition of these diseases as community health problems of major importance has been slow since the war-time fervor, but now in New York State[9] each county and city board of health is required by law to provide adequately for diagnosis, care, and treatment of persons with venereal diseases who are unable to pay for such attention. Discussion and consultative advice on the medical and public health aspects of syphilis have been made available to physicians and to county medical societies by representatives of the division of social hygiene and the state medical society of New York. They have also made arrangements for sending fluid from chancres to the laboratory for darkfield tests. The state is offering to detail nurses to physicians for investigating sources of infection and for the follow-up of lapsed cases. Free arsenicals are supplied to clinics and to those physicians treating for a nominal fee. The State of Massachusetts[10], also, has been coöperating with the physicians to the extent of supplying free arsenicals, printed information, and consultative service.

Health officers will take courage after hearing of two court decisions reported by Rail[11] of the Indiana State Board of Health. A woman who discontinued treatment without permission was finally located and placed in quarantine in the county jail. Action was brought to determine whether health authorities had the right to quarantine infectious venereal patients and whether the county jail was a suitable place. The court ruled that the patient was a menace to the public and should be confined, and since there was no more suitable place, the jail was proper. In another instance, the health officer quarantined a man because he refused to name the person from whom he contracted his disease. The judge ruled that the officer was within his rights in detaining the patient until the information was given. The man finally gave the woman's name and she was examined and found infected.

There have been some interesting legislative trends. A bill has been introduced into the French Senate[12] providing that the civil magistrate shall demand from all persons presenting themselves for marriage a physician's certificate specifying that the person has been examined within thirty days. Doubtless this bill will be more easily passed because it does not specifically mention the venereal diseases and provides that the results of the examination may not be revealed by the physician. Perhaps the failure of five of our states[13] to pass during 1931 measures requiring examination for venereal diseases before marriage was due to the unfortunate inclusion of the term "venereal diseases" which defeated its own end. The French bill provides only that the examination be made "with a view to entering on the marital relation." Some such bill has been sought in the Netherlands[14], but, though the Council of Health recognizes the value of such prenuptial examination, it doubts if the intervention of public authorities would be advisable.

The Medical and Surgical Director of the Baltimore and Ohio Railroad[15] realizes the danger to the public and to the property of the road in having men in their employ who may be syphilitic, and he checks very carefully for the existence of syphilis, especially neurosyphilis, among those in their service. Persons in a communicable stage are withdrawn, temporarily, from all classes of service; those with neurosyphilis are required to take treatment under the company's supervision and are not returned to engine or train service until there is assurance that the results of treatment are satisfactory. Locomotive engineers with neurosyphilis are permanently disqualified for road service. This is in line with the opinion advanced by Dr. Bla Joo[16] who believes that general paralytics, even in the state of complete remission following pyrexial treatment, may display greater or less defects and should not be treated by law as if they were normal beings. From the point of view of criminal tendencies, patients even with the most complete remissions have to be regarded as unaccountable, he thinks, for their acts and they should not be held legally responsible, but should be isolated and placed under observation, instead of arrest, should they come into conflict with the law.

The education of the laity and medical profession must continue if there is to be a permanent decline in syphilis. Physicians must learn to be suspicious not only of genital "ulcers", but of sores located anywhere because extragenital chancres are not uncommon. Cheever and Wheeler[17] record over one hundred mistakes in diagnosis and treatment of syphilis of those who have come to their attention within three years. As physicians become more "syphilis-conscious", we find in the literature more references to extragenital primaries. Nudemberg[18], writing in the *Semana médica,* Buenos Aires, describes five such chancres located in the suprahyroid region, on the index finger, on the upper third of the leg, in the pubic region, and on the chin.

Nelson of the Massachusetts State Health Department[19] shows the inconsistency of the attitude of most of the hospitals in this State in refusing to accept patients with a diagnosis of syphilis or gonorrhea while hesitating not at all to admit women with "pus-tubes" or men with prostatic abscess. Such institutions will admit to their maternity service a woman who is about

to give birth to a baby with syphilis in a highly communicable form. It is apparently a part of a prudish tradition, Nelson thinks, that these diseases were the result of "sin" and as such the victims were unworthy of consideration.

More attention is being given to prophylaxis. It is interesting to note that in Berlin[20] there are between 1,500 and 2,000 automats for the sale of prophylactics. In the United States Navy[6] a test of the efficiency of official prophylaxis was made. On one of the ships there were 251 exposures reported and 251 prophylactic treatments given, 187 of them within an hour after exposure, the longest interval being 10½ hours. After three months' observation the results noted were no syphilis, five cases of chancroid (prophylaxis was given from less than fifteen minutes after exposure to sixty minutes), gonorrheal urethritis two (one treatment was given five hours after exposure and the second five and one-half). The venereal rate of American troops in China[21] reached a high mark in 1930 of 566 per thousand. An intensive campaign was started which has brought about a remarkable decrease. In addition to the regular preventive treatment, each soldier was provided with a prophylactic packet and ordered to wear a condom. Inspection was held every forty-eight hours and all scratches and abrasions were treated with mercurochrome which was considered responsible for the decrease in chancroid infections, but, of course, was valueless for syphilis and gonorrhea. Hull[22] in discussing the prophylactic measures provided for the men in the British navy says that he believes the sheath is the best preventive known and should be issued to the men. The navy also provides the men with packets and treatment in ablution rooms with potassium permanganate and calomel cream, and if the men could be persuaded to make a more liberal use of these provisions, the author thinks there would be less disease. He considers that the antiseptic which gives the most promise of protection is samori, a disinfectant which gives off nascent carbonic acid in the form of a foam combined with oxychinol sulphate. The German merchant marine[23] has been waging a campaign against these diseases. They have issued for distribution to seamen with venereal diseases pamphlets containing treatment record sheets and information appropriate for use on vessels with and without ships' doctors.

As a preventive of congenital syphilis many measures, some of them drastic, have been suggested. Compulsory declaration of pregnancy[24] with penalties for failure to report has been proposed. The difficulties in the way of enforcement are obvious. When one considers that the records of the maternity department of Guy's Hospital[25] show that treatment with arsphenamine during pregnancy only, resulted in an increase of about 20 per cent in live births and a decrease of ten per cent in stillbirths, it would seem that the advantages of prenatal investigation and treatment would be self-evident, but there are many men in private obstetric practice who do not give their patients these advantages. For such, McCord's figures[26] should bring warning. In a series of 519 colored women with positive blood reactions at different periods of gestation, the pregnancies ended disastrously in six per cent of the treated cases as compared with 66.2 per cent of the untreated ones. Roentgen-ray examinations were made upon 73 dead babies of mothers with no treatment and 63 of them showed the characteristic change of congenital syphilis. Examination of 67 babies of treated mothers produced ten positive results, eight of which occurred in babies born of women who had received not more than seven treatments. In McCord's opinion safety for the baby demands not less than ten treatments during pregnancy, though, as Rutledge[27] declares, the earlier in pregnancy treatment is begun, the better are the chances for a healthy baby, but good can be accomplished by treatment as late as the eighth or ninth month. Rutledge goes so far as to say that every pregnant woman with a history of syphilis should receive treatment throughout gestation irrespective of the duration of her infection and of previous treatment or the length of time the blood reactions have been negative. Seemingly healthy wives of husbands with treated syphilis should receive treatment during pregnancy, especially if the husband's infection is of less than five years' duration. Spiegler[28] says that all women who have ever had syphilis should be treated during pregnancy unless the blood and spinal fluid examinations show that they are cured, but in his experience cases in which a cure has been demonstrated are so few that one might say that all women with a history of syphilis should be treated during pregnancy.

Research is trying to aid the cause of prophylaxis by means of drugs. Levaditi[29] thought that results might be obtained from a drug which is slowly eliminated and he tried bismuth. He found that it protected rabbits for at least 152 days, while Sonnenberg[29] made a clinical experiment on prostitutes. He gave 60 prostitutes weekly intramuscular injections of bismuth and used 50 untreated prostitutes as controls. Forty per cent of the untreated group acquired syphilis while only a little more than eight per cent of the treated girls developed the disease. Stovarsol (acetarsone), an arsenical to be given orally, which has been recommended as an unusually effective specific[30] is not approved by Kolmer and Rule[31] for the abortive treatment of syphilis in human beings.

For other use than for prophylaxis, stovarsol has been reported contradictorially, and the workers at the laboratory of the Research Institute of Cutaneous Diseases at Philadelphia[32] felt that the drug was worth careful study. They found that as ordinarily prepared it contained many impurities which may account for the inconsistency of results. After purification they found the toxicity low enough so that they feel it is probably useful for patients intolerant to the arsphenamine group. Of late some of the writers of recent articles recommend its use in congenital syphilis. Abt and Traisman[33] consider it the drug of choice with children because of its easy administration. Children must be watched during treatment, however, for Maxwell and Glaser[34] have experienced some severe reactions, even with one death in their series. Its usefulness in infants has been further endorsed by Rosenbaum[35], Mettel[36], and von Kiss[37]. Raiziss and Severac[32] find it satisfactory in experimental syphilis and capable of penetrating into the central nervous system and of use, probably, in neurosyphilis. Oppenheim[30] considers that it is indicated in laryngeal and pharyngeal gummata as well as in severe internal syphilitic affections and in the prophylaxis and treatment of paralysis and tabes.

For two years Gennerich[38] has been investigating a new mercury preparation, colloidal mercury sulphide. He finds it extraordinarily efficacious, well tolerated, and active. It may be used orally, intramuscularly, or intravenously, preferably the latter. It is intensely effective for all stages of syphilis, both clinically and serologically, but should not be used to displace arsphenamine, unless the latter is for some reason contraindicated, as it is less active.

A study of treatment results in the human patient is complicated and requires a very large amount of clinical material, more than is available for study in any one of the largest and best organized clinics, therefore Clark, Parran, and the chiefs of the clinics who had coöperated with the League of Nations in a health study a few years ago, decided to utilize the data, which had been compiled for that purpose, in a new detailed study of the value of the various drugs in the treatment of syphilis[39]. This is an extremely valuable contribution, but impossible for condensation to the limits of a review of this kind. Those interested will find the articles well worth reading.

In determining whether arsenicals can be given to a patient who has had arsenical dermatitis, Schoch[40] recommends the patch test with neoarsphenamine.

Bismarsen has been used on congenital syphilitic children and observed one and one-half to two and one-half years. It has given apparently valuable therapeutic results with good effect on interstitial keratitis[41]. We have had few reports on the use of bismuth in syphilis of the bones, but Wright[42] describes the healing of extensive osteomyelitis with intramuscular injections of potassium bismuth tartrate. The rapid fall of the fever and the improvement clinically indicate that this is as specific as the arsphenamines.

For cardiovascular syphilis the arsenicals in order of choice as given by Moore, Danglade, and Reisinger[43] are neoarsphenamine, bismarsen, and silver arsphenamine. Hazen[44] is convinced that carefully individualized thorough treatment, starting with mercury or bismuth, possibly combined with the iodides and later followed by alternating courses of the arsenicals and bismuth, definitely increases life expectancy for these patients. He advocates the close supervision of a competent internist throughout the course of antisyphilitic treatment. A critical review of the diagnosis and treatment of syphilis of the aorta and heart has been made by Coombs[45] and given with a bibliography of over two hundred references.

Atropin sulphate intravenously was used successfully in about thirty cases of tabetic crises[46] in doses of not more than three milligrams. Subcutaneous atropin and mercury cyanide intravenously have been used in tabetic atrophy with good results[47].

As a result of experiments made by Raiziss and Severac[48] the rabbit may now be utilized for the study of drugs and other curative agents on syphilis of the central nervous system. It has been discovered that spirochetes that have passed through generations of mice acquire the property of being able to penetrate into the brains of rabbits. Mice which had been inoculated with syphilis experimentally were found to show spirochetes in the inguinal and axillary glands in about 50 per cent of the cases[49]. The virulence of the glands did not correspond to the spirochete content. This is given as another argument in favor of the theory that syphilitic virus passes through an evolutionary stage that is infravisible before it reaches the visible and virulent stage represented by the spirochete. In inoculating experimental animals, the intracardiac route has been pronounced safe[50].

Martin and Leger[51] have applied their eight months' rule to a large series of cases and there has never been an exception. The rule is that after the last dose of arsenic has been given and the flocculation in the blood reduced to zero, an examination should be made monthly for eight successive months. If during that time there has been no recrudescence the patient can be pronounced cured.

The effect of attenuated virus on the chimpanzee as regards immunity is the basis of interesting studies[52]. The Truffi strain of syphilitic virus isolated in 1908 by subscrotal inoculation into rabbits from a human case was tested in

1914 and found pathogenic for monkeys, but less so for man, in whom at that time and in 1922 it caused only a papule not followed by primary or secondary lesions, although the serum reaction was positive. In 1931, after twenty-three years, the only form of inoculation that was virulent was a subscrotal graft tested on the chimpanzee and no ulceration followed. The authors are continuing their studies to determine whether its pathogenic activity can be still further weakened by passage through mice.

Two cases of sudden death from cisternal puncture[53] emphasize the fact that while technically not difficult, this operation requires experience which should be gained on the cadaver.

The League of Nations at a meeting in Geneva in September, 1932, made certain recommendations based on the results of the laboratory conferences held in Copenhagen in 1923, 1928, and in Montevideo in 1930: that whenever possible, two, and better still, three methods of testing blood should be used, one preferably being the Wassermann. If, for any reason, one method only is possible, a flocculation method may be used as the best ones proved superior to the best Wassermann tests in sensitiveness and their equals in specificity[54]. (A uniform international method of notation of results should be employed, in their opinion.) A new test of this sort has been described by Harry Eagle from the Syphilis Division of Johns Hopkins using sitosterol (corn germ sterol) as a fortifying agent[55]. In a test of 1600 serum specimens by the Kolmer, Kahn, and Eagle technics, Levine and Bromberg[56] found this new test practical as a laboratory aid in the diagnosis of syphilis with a reaction range not completely coincidental with the reaction ranges of either of the other two. The reading of weaker reactions was difficult but the frankly positive reactions were easy to evaluate. Bodansky[55] also found the Eagle test possessed a high degree of accuracy and reliability in a series of over 3,000 consecutive cases.

Hinton[57] has presented a third modification of his glycerol-cholesterol precipitation test which first appeared in 1927. In its modified form the test is more accurate and the technic simplified. The superiority of this test in the management of syphilis seems apparent from the fact that its positive reactions generally persist a third longer (sometimes twice as long) than positive Wassermann reactions, and neither rheumatic fever nor pneumonia appears to produce false positives. In a study of 161 cases of known syphilis in which 929 Hinton tests were made, there occurred only six per cent false negatives.

A study of 4,458 blood specimens using the Kahn and Kline tests[58] showed these tests in complete agreement in 98.9 per cent of all cases examined. The Kline test seems slightly more sensitive in treated cases and hypersensitive in cases with no antisyphilitic treatment, showing more false positives.

Because of the advantage of early diagnosis and hoping to find a test which would be positive earlier than the blood, Chargin, Eller, and Rein[59] experimented with the serum from chancres, using the microscopic slide precipitation test. Such tests had been attempted with the Wassermann and Kahn technics some years ago with no conclusive results. This time the results indicated that tests on fluid from local sores were less sensitive apparently than tests performed simultaneously on blood serum.

At the Peiping Union Medical College Hospital, Dorothy and Amos Wong[60] studied the milk and blood from 140 nonsyphilitic and 11 syphilitic women. They conclude that the Wassermann and Kahn tests of human milk are not sufficiently reliable to permit its use as an alternative for blood.

As a less hazardous agent for producing fever than malaria, radiotherapy has been introduced. Hinsie and Blalock[61], using an apparatus constructed on the same principle as a short-wave radiotransmitter excepting that the energy is concentrated between two condenser plates instead of being directed from an aerial, treated by this means 68 patients with general paralysis. Six months after treatment the results were remissions 12, improved 24, unimproved 26, died six, while the same number of patients treated with malaria gave remissions 13, improved 24, unimproved 21, died 10.

Interesting conclusions have been arrived at in several directions. Ruge[62] is inclined to believe that arsphenamine jaundice and catarrhal jaundice are the same disease. He analyzed 2,500 cases of the latter which occurred in the German navy from 1919 to 1929. He explains the greater number of cases among syphilitics as due to the weakened condition of the liver which has sustained syphilis and arsphenamine administration. O'Leary[63] finds after careful study of a considerable series of cutaneous late syphilis that approximately 50 per cent of these patients have demonstrable signs of visceral syphilis or neurosyphilis, but usually of a mild nature, thus exploding a very general erroneous idea that cases with late skin lesions do not have other types of late syphilis. A case of syphilitic involvement of the left common peroneal nerve occurring thirty-six years after the primary lesion[64] is extremely rare but is worth attention because of the danger of confusion with a neuritis due to numerous causes. Four cases of Charcot's disease of the knee have been reported in which solid bony fusion resulted in three so that the patients were able to walk without any artificial support. Cleveland and Smith, the au-

thors[65], hesitate to generalize from four cases but they hope the method will be tried by others.

While most physicians feel that it is dangerous to treat children with congenital syphilis during intercurrent secondary infections such as otitis media, bronchitis, or pneumonia, Lewin[66] thinks that there is much more danger of recurrences if treatment is not given than there is danger from the treatment in the presence of infection. He has often noticed the first signs of congenital syphilis developing during or immediately after an acute infection.

Malaria is on the increase in Indiana[67] and it has been suggested that there is a connection between the increase and the use of malaria as a therapeutic agent.

Contrary to the symptoms often quoted in textbooks, Hewer[68] finds that there is little evidence that increased cerebrospinal fluid pressure is either a common or reliable indication of syphilis of the nervous system.

For some years attempts have been made to decide whether or not yaws and syphilis are identical. Turner and Chambers[69] record their experience in transferring the virus of yaws to rabbits and monkeys. In inoculating rabbits with material from ten different patients with yaws, lesions developed after testicular inoculation, and the organisms were recovered after two passages through rabbits. Five monkeys were inoculated but there was no assurance that the organisms were transmitted, though lesions were produced. The absence of syphilis in Fiji, Solomon Islands, and New Guinea is considered due to wide distribution of yaws[2] which raises the question whether the treatment of this disease in the Pacific will not suppress or reduce this immunity.

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THE VINEGAR OF THE FOUR THIEVES

BY CHARLES H. LA WALL

Dean of the Philadelphia College of Pharmacy and Science

One of the eighteenth century glass stoppered shelf bottles in the ancient pharmacy of E. R. Squibb & Sons, exhibited this last summer at the Century of Progress Exposition in Chicago, is labeled *Acetum Bezoardicum.*

Now this name is unintelligible and untranslatable to the average member of either the medical or the pharmaceutical profession.

If one who is curious takes the trouble to look up the meaning of the word "bezoar" he will find that it applies to a concretion or calculus found in the intestinal tract of certain kinds of animals, particularly the herbiverous, and that it was once highly esteemed for its antidotal virtues.

If one consults a medical or pharmaceutical authority of the eighteenth century or earlier on the subject of bezoar, it will be found that the faith in the efficacy of this drug was so strong that it was believed that "no poison, no eruptive, pestilential or putrid disease, could resist its influence".

Satisfied with this definition the average investigator would dismiss the subject at this point with the assumption that *Acetum Bezoardicum* was a preparation of bezoar in vinegar (*acetum*). But there is a much more interesting tale connected with this name and with this preparation.

It is in reality made from aromatic spices and garlic, extracted with vinegar, and no "bezoar" entered into its composition at all, but the adjective "bezoardic" was intended to have a generic meaning of *antidotal*, as applied to this particular preparation, but to no other, for there were a number of preparations into which bezoar actually entered as an ingredient in the days when it was held in high repute.

If the searcher looks still further he will find that it was called "*Gewürz Essig*" (spice vinegar); "*Pest Essig*" (plague vinegar); "*Acetum Prophylacticum*" (prophylactic vinegar) and "*Vinaigre des Quatre Voleurs*" (vinegar of the four thieves), and that it had a most unusual history.

The story told of its origin is that during an epidemic of "the plague" in Marseilles in the early part of the eighteenth century, four robbers, by the use of this prophylactic, attended without harm hundreds of dead and dying citizens, and under the guise of these disinterested services they robbed their victims; and that one of them upon being caught confessed their crimes and saved himself from punishment by divulging the composition of the preventive they had employed to pursue their nefarious practices.

The belief in this fanciful tale was so strong that the preparation soon attained a wide sale in both Europe and America and this sale continued for more than a century.

The interesting part of the story is that a modified form of this same remedy is still official in the National Formulary of the United States and in a number of foreign pharmacopoeias as well under the name of Aromatic Vinegar.

CASE RECORDS
of the
MASSACHUSETTS GENERAL HOSPITAL

ANTE MORTEM AND POST MORTEM RECORDS AS USED IN WEEKLY CLINICAL-PATHOLOGIC EXERCISES

EDITED BY RICHARD C. CABOT, M.D.
F. M. PAINTER, A.B., ASSISTANT EDITOR

CASE 20021

PRESENTATION OF CASE

DR. ROY B. COHN:* *First admission.* A forty-seven year old married Canadian teamster entered for the first time fourteen years before his fifth and last entry.

Eleven months before admission he noticed that he was developing great difficulty in reading. One month later he was forced to give up his work as driver of a laundry wagon because of inability to read the score book. This impairment in vision became steadily worse. In addition he began to have four or five periods a day during which he was unable to see anything. These periods were associated with headaches and pain beginning in the eyes and extending downward to the back of his neck. They were not accompanied by dizziness, nausea or vomiting. These attacks of blindness began as though a blanket had been thrown over his eyes, and after five or six minutes the clouds spread from within outward. The left eye was from the start more affected than the right.

His family, marital and past histories are irrelevant.

Physical examination showed a well developed and fairly obese man. The chest and abdomen were negative. The fundi showed pale disks with clean cut edges. He had momentary sensations of foul odors. Neurological examination showed bilateral hemianopsia, slight deafness of the left ear and slight deviation of the tongue to the right.

X-ray examination showed a definitely abnormal sella turcica. The posterior clinoid process was not visible. The floor appeared to be thin.

A blood Wassermann was negative. The spinal fluid showed twenty cells and positive alcohol and globulin tests.

He was discharged to return later for operation.

Second admission, three weeks later. Operation was performed. His postoperative course was uneventful and he was discharged relieved.

History of interval. He was followed in the Outpatient Department after his discharge. His left eye improved very much. His right eye, however, remained in the same condition. Two days before readmission he fell on his head, and following that had a discharge of cerebrospinal fluid from his nose at intervals.

Third admission, six months after his second discharge.

He remained in the hospital for about a week, during which time the nasal discharge stopped. He was given a series of x-ray treatments, following which his visual acuity increased. He was discharged at the end of six days.

History of interval. He was followed in the Outpatient Department for the next eight years and the following notes were made.

Three years after the third discharge his memory was slightly impaired. Vision of left eye 20/40, of right eye 20/200. He was given more x-ray therapy.

A year later he was symptomless.

The next year he fainted on two occasions without warning. He was given more x-ray therapy.

The following year he had many petit mal attacks without warning.

During the next year he had three attacks. There was only very poor sight in the right eye. He was given more x-ray therapy.

Fourth admission, eight years after his third discharge.

On admission to the wards he was markedly drowsy and showed a partial loss of memory. At other times he was markedly euphoric. The vision of the right eye was 20/200, that of the left eye 20/20. His sense of smell was subjectively diminished. On the right his hearing was a little dull. There were no other abnormalities in his neurological examination.

He was given an x-ray treatment and discharged at the end of a week.

History of interval. During the next five years he was followed in the Outpatient Department. The following notes were made.

A year after his fourth discharge the light perception in the right eye was gone. The left eye was apparently normal. He was inclined to be moderately euphoric.

One year and again three years later no change was noted in his visual fields.

The following year, a month before his fifth entry, his epileptic attacks began to increase in number, occurring almost daily. His euphoria became more marked.

Fifth admission, five years after his fourth discharge.

Physical examination on admission to the wards showed a very heavy man in no apparent distress. The left eye was normal. The right had been displaced caudally and showed slight external strabismus. There was no extra-ocular muscle impairment. The right disk was very pale and atrophic; the left was not remarkable. The vision in the right eye remained only in the upper nasal quadrant of the field. The other cranial nerves were normal. He was still rather talkative and euphoric. His reflexes were all sluggish.

*Resident on the Neurosurgical Service.

A lumbar puncture was normal except for positive alcohol and ammonium sulphate tests.

Operation was performed. He did poorly postoperatively and died the following day.

Clinical Discussion

Dr. Cohn: The operation at the second admission was a frontal osteoplastic craniotomy. The brain bulged strongly on opening the dura. The pituitary was exposed with much difficulty. In the pituitary region there appeared to be a fairly large new growth, the anterior portion of which was removed. During the operation the frontal lobe was considerably torn. The dura could not be resutured. The orbital ridge and bone flap were replaced.

Dr. George W. Holmes: These films are not from our laboratory. Those of you who are near enough can see the broad sella with absence of the posterior clinoid.

These films were taken here. This is the site of the operative field. There is a dense shadow below it that may be a fragment of bone or a localized area of calcification. The posterior clinoids are gone. There is calcification here, about which I am not certain. Such extensive erosion of the posterior clinoids without involvement of the anterior clinoids would suggest a tumor outside the sella. On the other hand a tumor outside the sella that destroyed the posterior clinoid processes would also cause increased intracranial pressure, which this has not done. So we have to assume that the tumor is either within the sella or close to it. A tumor in another part of the brain pressing downward and destroying the clinoid processes by pressure would also show prominent skull markings. It is possible that the decompression operation prevented the formation of that evidence.

Dr. W. Jason Mixter: This history goes back quite a long way. If I remember rightly it was the first transfrontal operation that I ever did on a pituitary tumor, one of the very early ones at any rate.

There is one interesting point that comes up in regard to the operation which has not been brought out, that is that the technic used at that time called for removal of the supraorbital ridge in order to give one a more direct exposure of the chiasm under the frontal lobe. We have since found that such a procedure is unnecessary and it has been given up. It was done however in this case and the supraorbital ridge, a more or less wedge-shaped piece of bone about 2.5 or 3 centimeters in greatest diameter, was removed and set aside to be put back again at the end of the operation. Unfortunately, due to some oversight during the operation the piece of bone was thrown into the bucket with the dirty sponges. We were a little nonplussed to know what to do about it, but we put it into the instrument boiler and boiled it and put it back in again. I do not know how much in the way of the use of boiled bone had been done at that time. It caused no trouble except a little displacement downward, which accounted possibly for the downward displacement of the eye throughout the rest of his life.

That is the most interesting thing that happened in the early days. I think it is quite interesting to know that that piece of bone should have remained in his skull, or have been replaced in his skull by living bone, throughout this period of time.

Dr. Tracy B. Mallory: Dr. Putnam, will you tell us about your findings at the last operation?

Dr. Tracy J. Putnam: This patient's condition and also his family's condition were pretty desperate and seemed to us to demand a desperate remedy. It seemed to us there was not a great deal of chance that we could get out the rest of the tumor, which had obviously grown a great deal since the first operation, because his condition was becoming progressively worse.

The first thing that attracted my attention on reopening Dr. Mixter's old wound was a large cyst replacing perhaps two-thirds of the right frontal lobe. This communicated with the ventricle and was crossed by a few filmy spider-web-like strands floating in fluid. When these were brushed away it was possible to see the tumor, which was perhaps the size and color of a plum, slightly flattened over the floor of the skull. Through it ran the right optic nerve, and I gently dissected it. It ran into both temporal lobes and the left frontal lobe. I proceeded to dislocate it and to take off the small pieces. With one of these small pieces there came a tremendous amount of bleeding which I presume was from the anterior cerebral artery, which was entirely surrounded by the tumor. I controlled the bleeding by packing and backed out, but it was quite evident that he had not long to live.

Clinical Diagnosis

Recurrent pituitary tumor.

Anatomic Diagnoses

Adenoma of the pituitary, chromophobic type.
Arteriosclerosis: coronary, moderate; aortic, slight.
Obesity.
Intracranial hemorrhage, postoperative.
Operation: craniotomy and partial removal of tumor.
Atrophy of the frontal pole. Porencephaly?
Bone graft of skull.

Pathologic Discussion

Dr. Charles S. Kubik: There is a large funnel-shaped defect of the right frontal pole com-

municating with the lateral ventricle. The tumor is a large one, from 5 to 6 centimeters in diameter, occupying the region of the optic chiasm and extending upward and to the left, almost completely obliterating the third ventricle and pushing its way into the left temporal lobe. The optic chiasm is destroyed; the optic nerves and optic tracts are flattened and greatly diminished in size.

The sella turcica is enlarged to three or four times its normal size. Its floor is eroded. The anterior clinoid processes are spread apart and thinned out. The posterior clinoids are gone.

The piece of bone which was boiled at the time of the operation has the appearance of normal bone and there is firm bony union between it and the frontal bone.

DR. MALLORY: I will not show the sections, but the tumor is composed of the indifferent cells, that is, neither acidophilic nor basophilic, and slowly growing in type.

CASE 20022

PRESENTATION OF CASE

DR. THOMAS S. CLAIBORNE:* A forty-five year old single Greek leather worker entered with the complaint of fullness in the stomach and intermittent abdominal pain for the past three years.

Three years before admission he noticed that his abdomen was somewhat larger than usual, especially on the right side. This enlargement had increased, occasionally producing a sense of tightness and often associated with dull aching pain which was intensified on bending over. The pain was intermittent, occurring one day and absent the next. It never prevented him from sleeping, and in fact was less severe when he was lying down. There was no history of edema of the legs or body, although there was some question of puffiness of the face. He never noticed any change in color. Three physicians had told him he had chronic appendicitis. Two months before admission he first noticed an aching pain in the right shoulder region, present along the clavicle and up to the right ear. This pain was not constant and bore no particular relation to the abdominal pain. He had lost fifteen or twenty pounds during the past two months.

His appetite had always been good and had not changed. There had been no change in his bowel habits. There had never been any diarrhea, blood, or clay colored stools. From 1910 to 1928 he worked in a leather factory handling raw hides. Since then he had worked in a shoe factory until four months before admission, when he was discharged following a strike. For the past six or eight years he had been in the habit of drinking approximately one quart of home-made wine daily. He occasionally took alcohol. About thirty years before admission he was in bed for one week with a chest cold. There was no history of malaria, scarlet fever or typhoid fever. He denied venereal disease both by name and symptom. He was born in Greece, came to Massachusetts at the age of twenty-four, and had lived here ever since.

Physical examination showed a well developed and well nourished man in no acute distress. There was a slight icteric tint to the skin and sclerae. His teeth were very poor and there was fairly marked pyorrhea. Examination of the heart and lungs was negative except for soft apical and basal systolic murmurs. The blood pressure was 135/80. The abdomen was protuberant and except for the left lower quadrant was completely filled by the liver. The liver was very hard, irregular, and contained large nodules. Echinococcus crepitus could not be elicited. There was some tenderness in the epigastrium. One examiner believed that he felt the spleen, but was not able to rule out the left lobe of the liver.

The temperature was 99.8°, the pulse 90. The respirations were 20.

Examination of urine showed a specific gravity of 1.028 to 1.030. There was a positive test for bile. Examination of the blood showed a red cell count of 5,500,000 and a hemoglobin of 90 per cent. The white cell count was 8,500 with 64 per cent polymorphonuclears, 22 per cent lymphocytes, 9 per cent large mononuclears and 5 per cent basophiles. The platelets were normal. Examination of the stools showed the presence of starch, fat and muscle fibers. The guaiac test was negative. A Hinton test was negative. A liver function test showed 70 per cent retention. The icteric index was 20 and the van den Bergh 4.74 milligrams per 100 cubic centimeters, direct reaction. A gastric analysis showed free hydrochloric acid and was not remarkable. Both echinococcus fixation and skin tests were negative. The non-protein nitrogen was 25 milligrams, the carbon dioxide combining power 57.5 volumes per cent.

A gastro-intestinal x-ray series showed no definite evidence of disease of the esophagus, stomach or duodenum. The duodenal cap and the second portion of the duodenum showed a slight variation from normal, interpreted as being an extrinsic pressure defect. A barium enema was difficult to interpret because of poor visibility, which was believed to be suggestive of the presence of ascites. There was no definite organic lesion in the colon.

Ten days after admission an exploratory laparotomy was performed. The patient did fairly well following the operation, but on the eleventh day his temperature rose to 101, he became restless, and developed pain in his back. He failed rapidly and died two weeks after operation.

*Senior interne on the West Medical service.

Clinical Discussion

Dr. William B. Robbins: The only diagnostic point of special interest in regard to this case was that the man had taken care of animals as a child, had been closely associated with them, and had been working on hides and animal products ever since he had been in this country. These facts suggested the possibility of echinococcus cyst.

He had marked disturbance of liver function, with a large irregular liver, when we first examined him. I thought I could feel crepitus over some of these nodules, although they were distinctly hard. The diagnosis lay between possible echinococcus cyst and carcinoma of the liver.

We decided after talking it over with the surgeons that we would do a quick laparotomy to see if by any chance it was echinococcus. That seemed to be the only hope. If we could drain an abscess he might get relief. According to his story he had been rapidly getting worse during the past two months.

Laparotomy was done and carcinoma of the liver was found.

Clinical Diagnosis

Carcinoma of the liver.

Anatomic Diagnoses

Primary liver cell carcinoma.
Alcoholic cirrhosis of the liver.
Splenomegaly.
Thrombosis of portal and splenic veins.
Bile nephrosis.
Ascites.
Hydrothorax, right.
Jaundice.
Old cardiac infarct, posterior wall of the right ventricle.
Coronary occlusion with recanalization, right circumflex.
Operative wound, exploratory laparotomy.
External strabismus, right.
Corneal opacity ? right.
Dilatation of esophageal veins.
Pulmonary infarct.

Pathologic Discussion

Dr. Tracy B. Mallory: The liver which Dr. Miller came down on when he explored this patient fills this basin. It weighs over six kilos and shows not only a diffuse involvement of almost every part of the liver with carcinoma, but a definite cirrhosis in the few parts of the liver which are not infiltrated with the tumor. A small biopsy specimen was removed from which it was possible to make a diagnosis of primary liver cell carcinoma. That is of course supposed to be a very rare tumor, but in recent years large numbers of them are apparently being recognized in various places in the world. We certainly have had an unusual number here. I think there have been ten cases since I have been here, in a period of six years, at least an average of two a year; so it is common enough even in this region to be well worth considering in diagnosis.

Another entirely unexpected finding in this case was a complete thrombosis of the portal vein, obviously a very fresh and terminal lesion which had produced complete necrosis of the liver from the rapid and complete shutting off of blood in the last few hours of life.

The man also had a very irregular upper surface to his liver beneath the diaphragm, but no chest film was taken at any time, so I do not know whether the diaphragmatic shadow would have been irregular.

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EPIDEMIC ENCEPHALITIS

THE cases of encephalitis which were reported in epidemic numbers in St. Louis and Kansas City in August and September of 1933 should not be confused with those of lethargic encephalitis or "sleeping sickness" which occurred with such frequency throughout the civilized world ten to fifteen years ago. Leake[1] of the United States Public Health Service has called attention, in these cases, to the lack of ophthalmic symptoms, the practically uniform meningeal involvement and the prompt and complete recovery in the non-fatal cases. These characteristics agree with those of encephalitis "B," the name which Kaneko and Aoki[2] have given to cases of encephalitis which have occurred in epidemic form in Japan, particularly during August and September of 1919 and 1924. The Japanese workers consider lethargic encephalitis or encephalitis "A" to be an entirely different disease entity, characterized by slower and milder onset, longer duration, lower mortality, and the frequent presence of the Parkinsonian syndrome as a sequela. Histologically, the brain and meninges from cases of encephalitis "B" showed more diffuse lesions than the characteristic perivascular round cell infiltrations of encephalitis "A". In both, the demyelinization occurring in post-vaccinal encephalitis or that following other infections, such as measles, was lacking.

Although isolated workers have claimed that a filterable virus is the etiological agent in encephalitis "A," such claims have not been substantiated to the satisfaction of investigators in general. A far greater number of positive experiments have been carried out with material from cases of encephalitis "B". As cited by Kaneko and Aoki[2], spirochetes and Gram-positive diplococci have been isolated, both of which have been considered the causative agent by certain groups of Japanese workers. By far the majority of experimental work in Japan, however, has led the conclusion that encephalitis "B" is caused, primarily, by a filterable virus. Positive transfers of brain emulsion, cerebrospinal fluid and blood from human cases and brain emulsion from infected animals have been reported in rabbits, monkeys, rats, guinea pigs and mice. Berkefeld filtrates have been infective, as have glycerinized brain emulsions kept at icebox temperature for three months. Preliminary reports of animal transfer experiments with material from cases in this country have given results which also point to a filterable virus as the etiological factor. Muckenfuss, Armstrong and McCordock[3] have been able to transfer and establish the disease in monkeys and to retransfer to mice. Webster and Fite[4] have reported a high percentage of positive primary and secondary intercerebral transfers into a strain of mice known to be extremely susceptible to an infectious encephalitis of sheep. *Macacus rhesus* monkeys were susceptible, but the disease was not fatal, though transferable. Ordinary cultures of the infective material have been consistently sterile and Berkefeld filtrates have been infective.

Confirming Takaki[5], Webster and Fite have demonstrated the presence of specific protective substances in the sera from convalescent cases. Sera from normal adults in New York have failed to show protective qualities. Such findings suggest the use of convalescent serum as a therapeutic agent, but, in view of the questionable value of such serum in the treatment of anterior poliomyelitis, too much should not be expected.

REFERENCES
1 Leake, J. P.: J. A. M. A. 101:928, 1933.
2 Kaneko, R., and Aoki, Y.: Ergebn. d. inn. Med. u. Kinderh. 34:342, 1928.
3 Muckenfuss, R. S., Armstrong, C., and McCordock, H. A.: Pub. Health Rep. 48:1341, 1933.
4 Webster, L. T., and Fite, G. L.: Science. 78:463, 1933.
5 Cited by Kaneko and Aoki: *Loc. cit.*

THE BURDEN ON HOSPITALS IMPOSED BY AUTOMOBILE ACCIDENTS

Among the unpredictable needs for hospitalization, accidents resulting from the operation of automobiles occupy an important position, ranging from minor to the most important major operations.

Fortunately for the injured automobilists, reliable hospitals are not remote from the regular routes, and service is usually available and rendered promptly. With the discharge of the patient, the other side of the picture too often presents complications depending on the ability or disposition of the injured person to meet the charges of the hospital and attending physicians. Both disposition and resources of the recipient of care are often inadequate, involving a loss which too often the hospital and the doctor cannot afford.

Dr. John J. Moorhead of New York spoke of these unpaid accident charges as a "terrific financial strain on every community" in an address before the Interstate Postgraduate Medical Association of North America recently, and he suggested that appropriations taken from gasoline and road taxes should be made to hospitals to cover this financial burden. As an illustration we quote Dr. Moorhead:

"Suppose a man and his family from New York, Illinois, or any other state, come touring through your city. They have an accident. They are taken to one of your hospitals. They receive treatment that runs anywhere from a single dressing to two or three weeks of hospitalization or even more.

"They recover. They tell you they are grateful for the treatment, but have no money to pay. There is nothing the hospital can do about it. Everybody is just out of luck."

We wish to add to the above that any diversion of tax funds to pay for automobile accidents should include physicians as well as hospitals.

PROFESSOR SIGERIST AT THE BOSTON MEDICAL HISTORY CLUB

At the meeting of the Boston Medical History Club to be held at the Boston Medical Library, Monday, January 15*, Professor Sigerist will talk on his recent trip to Italy in search of medical manuscripts. Material of the greatest importance to doctors and medical historians, much of it unique and not previously published, will be presented. An opportunity is thus offered to the medical profession to hear a distinguished historian discuss in an informal manner a subject about which little is known. The medical manuscripts owned by the Boston Medical Library will be on exhibit. Of particular interest will be rare Hebrew manuscripts, recently acquired.

*See notice on page 115.

THIS WEEK'S ISSUE

Contains articles by the following named authors:

Lahey, Frank H. M.D. Harvard University Medical School 1904. F.A.C.S. Director, Lahey Clinic. Surgeon-in-Chief, New England Baptist Hospital. Surgeon, New England Deaconess Hospital. Address: 605 Commonwealth Avenue, Boston. Associated with him is

Jordan, Sara M. A.B., Ph.D., M.D. Tufts College Medical School 1921. Gastro-enterologist, Lahey Clinic. Associate Staff, New England Deaconess Hospital, New England Baptist Hospital and Robert Breck Brigham Hospital. Address: 605 Commonwealth Avenue, Boston. Their subject is "Cancer of the Stomach." Page 59.

Truesdale, P. E. M.D. Harvard University Medical School 1898. F.A.C.S. Surgeon, Truesdale Clinic, Fall River, Massachusetts. His subject is "Acute Pancreatitis—With a Review of Fifty-four Operative Cases." Page 66. Address: 151 Rock Street, Fall River, Mass.

Cary, Edward H. LL.D., M.D. University and Bellevue Hospital Medical College 1898. F.A.C.S. Professor of Ophthalmology and Otolaryngology, Baylor University College of Medicine. Emeritus Dean and Chairman of the Department, Diseases of Eye, Ear, Nose and Throat, Baylor University College of Medicine. President, American Medical Association, June 1932-June 1933. His subject is "The Public and Our Profession." Page 72. Address: 1717 Pacific Avenue, Dallas, Texas.

Root, Howard F. See page 44, issue of January 4, for record of author. His subject is "The Association of Diabetes and Tuberculosis. II. Pathology and Etiology." Page 78.

Nissen, H. Archibald and Spencer, K. A. See page 44, issue of January 4, for record of authors. Their subject is "Arteriosclerosis and Arthritis." Page 92.

Cheever, Austin W. A.B., M.D. Harvard University Medical School 1914. Assistant in Dermatology and Syphilology, Harvard Medical School. Assistant Dermatologist, Children's Hospital. Visiting Dermatologist, Beth Israel Hospital, Boston. Consulting Dermatologist, Framingham-Union, Waltham, Goddard, and Brockton Hospitals. His subject is "Progress in the Diagnosis and Treatment of Syphilis, 1931-1932." Page 97. Address: 472 Commonwealth Avenue, Boston.

MASSACHUSETTS LEGISLATIVE NOTES

The following described bills have been filed:

S. 16 is designed to regulate the practice of surgery, and reads:

A physician shall not remove any limb or organ of the body from a patient, without first obtaining consent of such patient, if the patient is mentally and physically capable of giving such consent; otherwise he shall obtain the consent of the patient's husband or wife or nearest available relative or of the patient's parents or guardian.

If such consent is not available, the physician may proceed upon his own judgment.

S. 5 provides that:

The board of health in cities and towns shall have authority to fix the territorial limits or milk shed within which milk shall be produced before licenses may be issued for the sale thereof. In case of an emergency or milk shortage, the milk inspector or other licensing authority may, if necessity and convenience require, grant licenses to suitable persons although the milk is produced beyond the prescribed milk shed or territorial limits.

H. 103 is an Act relative to Workmen's Compensation Insurance Policies, Mergers of Insurance Companies, and Certain Insurance Brokers' Licenses issued to Partnerships, and is also relative to certain obligations of the Insurance Companies.

H. 101 is an act relative to providing Compensation under the Workmen's Compensation Law for Children of Deceased Employees in Case there is no Surviving Dependent Parent, and reads as follows:

If there is no surviving wife or husband of the deceased employee, such amount or amounts as would have been payable under this section to or for the use of a widow and for the benefit of all the children of the employee, shall be paid in equal shares to all the surviving children of the employee.

H. 31 reads:

Whoever sells arsenic (arsenious acid), atropia or any of its salts, chloral hydrate, chloroform, cotton root or its fluid extract, corrosive sublimate, cyanide of potassium, Donovan's solution, ergot or its fluid extract, Fowler's solution, oil of pennyroyal, oil of savin, oil of tansy, Paris green, Parson's vermin exterminator, phosphorus, prussic acid, "rough on rats," strychnia or any of its salts, tartar emetic, tincture of aconite, tincture of belladonna, tincture of digitalis, tincture of nux vomica, tincture of veratrum viride, compounds of fluorine, or carbolic acid, shall affix to the bottle, box or wrapper containing the article sold, a label of red paper upon which shall be printed in large black letters the name and place of business of the vendor and the words "Poison" and "Antidote," and the label shall also contain the name of an antidote, if any, for the poison sold.

This bill has to do with the restriction and control of the sale of such articles.

H. 127 provides for a change in Section 66 of Chapter 111 of the General Laws in that the charges for the support of an inmate in a state sanatorium shall be seven dollars per week to be paid quarterly and provision for collecting charges of indigent inmates if or when such may be able to pay with certain specified obligations of kindred or towns.

H. 126 provides in substance for the compulsory vaccination of pupils in private as well as public schools.

H. 156 is relative to increasing the Payments for Deaths resulting from Industrial Accidents, and reads as follows:

Section thirty-one of chapter one hundred and fifty-two of the General Laws is hereby amended by inserting in place of "ten dollars" per week the amount of "fourteen dollars" per week and in place of "twelve dollars" per week the amount of "eighteen dollars" per week, and in place of "two dollars" more per week the amount of "four dollars" more per week; that the provision that in case any such child is a child by a former wife, the death benefit shall be divided between the surviving wife and all living children of the deceased employee in equal shares, the surviving wife taking the same share as a child be stricken out and the following words inserted therein: — provided, that in case any such child is a child by a former wife, the death benefit shall be paid as follows: the surviving wife shall receive fourteen dollars per week and all living children of the deceased employee entitled to receive compensation under section thirty-two shall each receive four dollars per week, but said children shall not receive more than the total of eighteen dollars per week,— that the words "if and so long as there are five or less, three dollars a week" be stricken out; and that starting with the paragraph "In all other cases of total dependency," the words "but not more than ten dollars nor less than four dollars a week" be stricken out and the following words be inserted in place thereof:— but not more than eighteen dollars nor less than fourteen dollars a week,—and the words "sixty-four hundred dollars" be inserted in place of "four thousand dollars".

H. 147 is a draft of an act to make uniform the law with reference to narcotic drugs.

H. 125 is based on the report of the Board of Regulation in Optometry, and recommends changes in the time for meetings, better

definition of the practice of Optometry and a suggestion that the board shall have power to make extended rules and regulations relating to the practice of Optometry.

The Massachusetts Medical Society

AN URGENT PROTEST ADOPTED AT A MEETING OF THE COMMITTEE ON PUBLIC RELATIONS HELD IN BOSTON, JANUARY 2, 1934

Whereas, the Civil Works Administrator of the United States, Harry L. Hopkins, has instructed John J. Morris, Counsel for the Civil Works Administration of Massachusetts, to place all employees injured in the Civil Works program under the Federal Compensation Act and

Whereas, this procedure is antagonistic to the Massachusetts Law for workmen's compensation in so far as it deprives the injured workman of the right to select his own physician,

Be it resolved that the Massachusetts Medical Society, composed of four thousand and nine hundred Massachusetts physicians, acting through the Committee on Public Relations, protest the application of the Federal Compensation Act to the Civil Works program in Massachusetts and

Be it further resolved that we respectfully urge that the man injured in Civil Works program has the right to select his own physician.

Members of the Committee present were Dr. William H. Robey, Dr. Elmer S. Bagnall, Dr. John H. Blaisdell, Dr. William G. Curtis, Dr. Fred R. Dame, Dr. Francis H. Dunbar, Dr. Walter A. Lane, Dr. William F. MacKnight, Dr. Stephen A. Mahoney, Dr. Richard A. McGillicuddy, Dr. Charles E. Mongan, Dr. P. J. Sullivan, Dr. M. A. Tighe, Dr. J. I. B. Vail and Dr. Harper E. Whitaker.

After adoption of this protest, it was voted to send a copy to the following:

Franklin D. Roosevelt, President of the United States

Harold L. Ickes, Secretary of the Interior

Harry L. Hopkins, Relief Administrator

David I. Walsh, Senator of Massachusetts

Marcus A. Coolidge, Senator of Massachusetts

Representatives of Massachusetts, 1-15 Districts

Olin M. West, Secretary, American Medical Association, 535 North Dearborn Street, Chicago, Illinois

Morris Fishbein, Editor, *Journal of the American Medical Association*

William C. Woodward, Bureau of Legal Medicine and Legislation, American Medical Association, Chicago

Dean Lewis, President, American Medical Association, Johns Hopkins University, Baltimore, Md.

RECENT DEATHS

KOTLER — Moses G. Kotler, M.D., died on January 7 at the Malden Hospital after an illness of less than a week. He was thirty-eight years of age. For nearly two years Dr. Kotler had been city physician of Malden, and it is said that overwork in this capacity contributed to his early death. During the World War he served with the Students' Army Training Corps and later was attached to the Veterans' Bureau in Washington.

Born in Russia, Dr. Kotler came to America when very young and was educated in the Boston public schools. He later attended Tufts and was graduated from the Tufts Medical School in 1920. He is survived by a widow, Mrs. Anna G. Kotler; two children, Alvin, 9, and Theodore 5; his parents, Mr. and Mrs. Harry Kotler of Dorchester, and one sister, Mrs. Ruth Shimberg, also of Dorchester.

STONE—Byron Stone, M.D., died suddenly at his home in White Village on December 28, at the age of eighty-two years. He was born in North Oxford, and after graduating from the Oxford High School, attended Worcester Academy and Worcester Polytechnic Institute. He received his medical degree at Jefferson Medical College in 1877, and had been a practicing physician for fifty-six years.

DIKE — John Dike, M.D., a graduate of Bowdoin College in the class of 1880 and of the Boston University School of Medicine in 1888, died at his home in Melrose on January 2, after a short illness. He had been for forty-five years a practicing physician of Melrose, where he was formerly a member of the school committee and served a number of terms as a member of the board of aldermen and as its president. He was at one time chairman of the Melrose Republican City Committee.

Dr. Dike is survived by his widow, Mrs. Mary Dike; four sons, Donald, Eben, Samuel W. and John K. Dike; one daughter, Miss Mary K. Dike, and nine grandchildren.

DOY — Wilberforce Clarkson Doy, M.D., died at his home, 1384 Commonwealth Avenue, Allston, after an illness of four months, at the age of eighty-two years. Born in Rochester, New York, Dr. Doy was a graduate of the Cleveland Medical School and had been a local practitioner for fifty years. He is survived by his widow, a brother, William S. Doy of Battle Creek, Michigan, and two nieces.

NOTICES

AWARD

The New England Society of Psychiatry, at its next Spring meeting, will make two awards, one of $100.00 and one of $50.00, to the writer (or writers) of the best papers completed or published during the calendar year of 1933 embodying research in psychiatry by a younger worker (or workers.) Phy-

sicians, psychologists, social workers, or others are eligible. Membership in the Society is not a requisite.

Writers who have once received an Award are not again eligible. Seasoned writers, senior physicians, or heads of departments in which there are junior workers, while not inevitably excluded, will not generally be regarded as eligible for the Awards.

The work on which the papers are based should preferably have been done in New England or by workers now living in New England.

The papers will be examined by a Committee of three members who are accustomed to reviewing papers, and by the Executive Committee of the Society. They will be judged on the basis of their scientific quality.

Copies of articles or marked copies of journals in which the articles appeared should be sent before February 1, 1934, to the Secretary of the Society.

Superintendents of institutions, public or private, for the care of mental patients in New England are requested to post this notice and to send to the Secretary a list of such papers published by the members of his staff as he thinks entitled to be considered for the Awards.

HARLAN L. PAINE, M.D., *Secretary.*

North Grafton, Mass.

RADIO HEALTH MESSAGES

JANUARY-FEBRUARY-MARCH, 1934

Sponsorship: Public Education Committee of the Massachusetts Medical Society and Massachusetts Department of Public Health.

Courtesy WBZ. Fridays, 4:30 P.M.

Jan.
12 Prevention Pays A Premium
19 Hypertension
26 The Common Cold

Feb.
2 What A Parent Should Know About Measles
9 Milk
16 Stomach Trouble
23 Lumps in the Neck

March
2 Age and Cancer
9 Some Problems of Epilepsy
16 Fractures
23 How to Keep the Well Child Well
30 Résumé of the Year's Work

HEALTH QUESTION BOX

Sponsored by Massachusetts Department of Public Health. Fridays 4:40 P.M.

RADIO HEALTH FORUM

Queries from the public are answered under the sponsorship of the Department of Public Health.

Courtesy WEEI. Fridays, 5:00 P.M.

Questions on Health and Prevention of Disease may be sent to: Radio Health Forum, State Department of Public Health, State House, Boston.

SPECIAL

Beginning Friday, January 19, the State House Broadcasts will be discontinued and in their place will be substituted Ten Minute Health Reviews.

Sponsored by the Massachusetts Department of Public Health. Assisted by Miss Violette Babcock, Violinist, and Mr. G. Lambert Roscoe, Pianist and Organist.

Courtesy WEEI. Fridays, 1:15 P.M.

Glimpses into the History of Public Health in Massachusetts together with the Functions and Activities of the Massachusetts Department of Public Health, Blended with Classical Music.

After hearing this new program we would appreciate your comments.

REPORT AND NOTICES OF MEETINGS

THE HARVARD MEDICAL SOCIETY

The Harvard Medical Society met in the amphitheatre of the Peter Bent Brigham Hospital on Tuesday, December 12, at 8 P.M. Dr. David Cheever was chairman of the meeting. The subject for the evening was "The Thyroid Gland in Health and Disease." This was introduced by the presentation of two cases illustrating different aspects of thyroid disease.

The first case was that of a forty-eight year old woman who at the age of twenty-four had had an attack of pain in both knees associated with swelling, redness, and tenderness. Ten years ago she developed progressive swelling of the neck which improved on treatment with iodine. Three years ago she showed dyspnea, swelling of the ankles, and palpitation. More recently she manifested abdominal distention and, shortly before entering the hospital, she became orthopneic. Lately, although her appetite has been voracious, she has lost considerable weight. The physical examination disclosed marked venous congestion of neck and upper extremities. The right lobe of the thyroid was greatly enlarged and displaced, the sternocleidomastoid anteriorly and to the right but there was no fixation. Systolic and diastolic bruits were heard over the thyroid. The heart was enlarged to the anterior axillary line. An irregular rhythm, pulse deficit, and rough diastolic murmur were noted. An edema extended up to the flanks. The basal metabolic rate has varied between +55 and +34. Administration of digitalis produced marked improvement with disappearance of edema. Iodine treatment has now been instituted.

The second case was that of a thirty-five year old woman who developed swelling in the neck and nervousness a year or two after taking a position as a telephone operator at the age of seventeen. Her symptoms progressed and at the age of twenty-four she was admitted on the Surgical Service at the Brigham Hospital with palpitation, nervousness, sweating, and diarrhea. Her hair was gray and

her skin showed a salmon-pink color. The artery supplying the superior pole of the thyroid was ligated with subsequent temporary improvement. Subtotal thyroidectomy was followed by somewhat more lasting improvement. At the age of thirty she returned to the hospital and was treated with Lugol's solution which gave symptomatic relief. She recently reëntered the hospital on the Medical Service with a complaint of anorexia. Her gray hair and salmon-pink skin were striking. A bruit was heard over the thyroid. There was slight exophthalmos but no other accompanying eye signs.

The cases were discussed by Drs. Fitz, Levine, and Means. Dr. Fitz briefly recounted the history of hyperthyroidism from its clinical recognition by Parry, Graves, and Basedow to our present conceptions regarding manifestations and treatment of thyroid disease. In connection with the first case Dr. Levine observed that, although hyperthyroidism and rheumatic heart disease are often associated, rheumatic fever is not common in myxedema. He raised the question whether the observation had any significance. Dr. Means stated that the infrequency of rheumatic heart disease in myxedema is explained by the fact that myxedema itself is not a common disease. He then discussed the first case presented in some detail and cast considerable doubt on the diagnosis of thyrocardiac disease. He believed it unlikely that a thyrocardiac with gross anasarca would have lost all edema on digitalis alone. He stated that the heart in this patient was larger than any he had ever seen in thyrotoxicosis. He expressed the opinion that a thyrotoxic heart does not occur unless a patient already has heart disease of some other sort.

The first speaker of the evening was Dr. William T. Salter, who gave a clear and concise discussion of the "Chemistry of the Thyroid Hormone." The thyroid gland was described as a "trap" for the iodine taken into the body. It shows an increased iodine content within five minutes after the ingestion of potassium iodide and a considerable part of the iodine intake can be recovered from the thyroid the next day. The so-called colloid contains about 90 per cent of the gland's iodine. The remaining 10 per cent contained in the supporting framework is known to be inactive. The iodine of the colloid forms a part of thyroglobulin, a complex protein molecule containing thyroxin and di-iodo-tyrosine. The latter often accounts for two-thirds of the iodine present in the colloid, while thyroxin is responsible for only one-third.

Dr. Salter then cited evidence both from animal experiments and from observations on man made by Drs. J. H. Means and Jacob Lerman to show that, if not actually a hormone in itself, di-iodotyrosine plays an important part in the active principle of the thyroid gland. Thyroxin itself is rather insoluble near the neutral point and oral administration is known to be very unreliable. Dried thyroid given orally, however, is very efficient as is thyroxin injected intravenously. A polypeptide obtained by enzyme action (trypsin) on thyroglobulin is effective both orally and parenterally. With pepsin, thyroglobulin is split into peptones containing thyroxin and di-iodo-tyrosine, respectively. The fraction containing the latter is inactive. Administration of the two together in thyroglobulin combination, however, is far more effective than the thyroxin fraction alone. Thus, the activity of thyroid material is best judged, as Dr. Reid Hunt suggested years ago, by its total content of iodine and not by its thyroxin content.

The next speaker, Dr. S. Hertz, recounted the results of his work done at the Massachusetts General Hospital in collaboration with Dr. Alfred Kranes in a report entitled "The Effect of Anterior Lobe Hormones on Thyroid and Parathyroid." Extracts from the urine of pregnancy were found to have no effect on the thyroid in rabbits. Injections of acid and alkaline extracts of the anterior lobe of the pituitary gland, however, were followed within twenty-four hours by a conspicuous hyperplasia. Continued injections caused disappearance of the colloid so that the histological picture closely resembled that of marked Graves' Disease. Long-continued injections of the hormone, however, led to involutional and atrophic changes in the thyroid. Other workers (Evans and Szarka) have shown in rats that injections of pituitary extract lead at first to an increased oxygen consumption followed by a fall after prolonged administration. It has been proved that the extract does not act directly to change the oxygen consumption but indirectly through its effect on the thyroid. The histological sequence described was adduced as an explanation of the metabolic data and the clinical application of the method of pituitary overtreatment for thyroid exhaustion was raised as a rational possibility in the treatment of Graves' Disease.

Dr. Hertz then described the changes produced in the parathyroids by injections of the anterior lobe extracts. There is marked hyperplasia of the glands with the appearance of mitotic figures in histological sections. Rabbits treated with sterile unheated anterior lobe extract developed marked atonia which failed to appear when heated extract was used. No exhaustion phenomena have been found as yet in the parathyroids as in the thyroid after continued treatment.

The next report was presented by Dr. J. Lerman, who discussed "Total and Thyroxin Iodine in Relation to Dosage of Thyroid." He observed that in the treatment of thyroid insufficiency there is no substitute better than desiccated whole thyroid gland. Difficulties arise, however, in standardization of the various commercial preparations. Six preparations from four well-known commercial houses were studied in various combinations on hypothyroid patients and their potency judged by their effect on the basal metabolic rate. The following dosages of the different products when admin-

istered orally were found equivalent to one-third milligram of thyroxin given intravenously:

Armour	1.5 grains
Lederle	1.5 grains
Parke Davis	1.0 grains
Burroughs and Wellcome	5.0 grains

The above difference between the various thyroid products has to be borne in mind in the treatment of myxedema or cretinism. Correlating the potency of the substances with their iodine content, Dr. Lerman showed that total iodine rather than thyroxin iodine is the important factor. Work in other clinics has shown that in normal patients and animals thyroxin is more efficient than desiccated thyroid according to iodine content. Since these experiments were done in normal patients and animals, however, they are probably not applicable to the human being with myxedema.

The last speaker, Dr. James H. Means, described "Some Atypical Clinical Pictures of Thyrotoxicosis." He declared that, although a typical case of thyrotoxicosis is the simplest clinical diagnosis that can be made, in some cases there may be one predominant symptom which masks the rest of the picture and leads the physician astray. Moreover the symptoms in hyperthyroidism vary considerably. They are different in men and women, the former sometimes having almost no complaints. In youth the nervous symptoms are the more prominent, whereas, in older people the more important symptoms are referable to the cardiovascular system. In elderly patients the classical fine tremor is often changed to a coarse one. Dr. Means called attention to the fact that thyrotoxicosis may occur in childhood with a normal basal metabolic rate which he illustrated by citing a misdiagnosed case. He then reviewed a case in which there was so much muscular atrophy, atonia, and fibrillary twitching that a diagnosis of progressive muscular atrophy was made. The basal metabolic rate, however, was +58 and there was a typical improvement with potassium iodide treatment. In this case, the prominent myasthenia had masked the underlying picture of thyrotoxicosis. Another patient had gastro-intestinal symptoms to so marked a degree that diagnoses of gall-bladder disease, ulcer, malignancy, and cirrhosis were made. The basal metabolic rate was +58. Marked improvement followed subtotal thyroidectomy. Still another case cited was that of a sixty year old bachelor with dyspnea, cough, edema, smooth tongue, anemia, and achlorhydria. There was a question of jaundice in the patient's history. The diagnosis evoked considerable debate but a typical response was shown to potassium iodide, and preparation is now being made for subtotal thyroidectomy. In closing, Dr. Means emphasized the importance of the diagnostic use of potassium iodide in cases where the diagnosis was in doubt.

After the papers had been discussed by Drs. Cheever, Fitz, and Aub, the meeting was adjourned by Dr. Cheever.

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The regular clinico-pathological conference of the New England Hospital for Women and Children will be held at the hospital, Dimock Street, Roxbury, on Thursday, January 18, at 8 P.M. The following cases will be reported: Hypertension with Fibrillation; Carcinoma of the Gastro-Intestinal Tract; Pyloric Stenosis.

In February and March the clinical conferences will be held in conjunction with the staff meetings on the first Thursday evening of each month, beginning at 7:30.

ALICE H. BIGELOW, M.D., *Secretary.*

BOSTON CITY HOSPITAL

STAFF CLINICAL MEETING

Thursday, January 18, 1934, at 8:15 P.M.
Thorndike Amphitheatre

1. Nutritional and Infectious Bone Diseases. Dr. Albert M. Moloney.
2. Pre- and Post-Operative Radiation in Breast Carcinoma. Dr. Frederick W. O'Brien.
3. Colonic Lesions Including Amoebic Dysentery. Dr. Max Ritvo.
4. Interpretation of Cardiac Displacements. Dr. Paul F. Butler.

COMMITTEE ON HOSPITAL CLINICS.

AMERICAN PUBLIC HEALTH ASSOCIATION

The American Public Health Association announces that its Sixty-third Annual Meeting will be held in Pasadena, California, September 3-6, 1934. The Western Branch of the American Public Health Association, with a membership of more than 1,200 from eleven western states, will hold its Fifth Annual Meeting at the same time.

Dr. J. D. Dunshee, Health Officer of Pasadena, has been appointed Chairman of the Local Committee on Arrangements. He will be assisted by Dr. John L. Pomeroy, President, and Dr. W. P. Shepard, Secretary, of the Western Branch, and other prominent public health authorities on the west coast.

NEW ENGLAND PHYSICAL THERAPY SOCIETY

The regular meeting of the New England Physical Therapy Society will be held in the Banquet Hall of the Hotel Victoria, 271 Dartmouth Street, Boston, at eight o'clock on the evening of January 17, 1934.

This meeting will be conducted by Dr. Frederick H. Morse.

PROGRAM

Threatened Colon Malignancy. Frederick H. Morse, M.D., Boston.

Discussion will be opened by Dr. William G. Curtis.

Dr. Morse's authority to speak on this subject is well known. He is returning from Florida to present this program which deserves a large attendance.

Council meeting at 6 P. M.; Round Table Dinner at 6.30.

All members of the medical profession are cordially invited to attend and to participate in the discussion.

ARTHUR H. RING, M.D., *Secretary.*

HARVARD MEDICAL SOCIETY

The next meeting of the Harvard Medical Society will be held in the Peter Bent Brigham Hospital Amphitheatre (Van Dyke Street entrance), Tuesday evening, January 16, at 8:15 o'clock.

PROGRAM

Presentation of Cases.

"A Trip to the East Coast of Greenland." By Dr. W. G. Smillie with motion pictures.

JOHN HOMANS, M.D., *Secretary.*

BOSTON MEDICAL HISTORY CLUB

John Ware Hall, 8 Fenway
Monday, January 15, at 8.15 P.M.

"A Trip Through Italy in Search of Medical Manuscripts." Dr. Henry Sigerist, Professor of the History of Medicine and Director of the Institute for the History of Medicine, Johns Hopkins University.

Your attention is called to the free course on Medical Bibliography now being given by the Boston Medical Library. The lectures will be held on January 19, 23, 30, February 6 and February 13. For further information, apply at the Library.

JAMES F. BALLARD, *Secretary.*

BOSTON MEDICAL LIBRARY

ANNUAL MEETING

The Annual Meeting of the Library will be held on Tuesday evening, January 16th, at the Library, 8 The Fenway, at 8.15 o'clock in Sprague Hall.

Following the business meeting Dr. Fred B. Lund will give a talk entitled "Galen's Comments on the Game of Ball."

"Some Responses of the Body to High Temperature." Dr. Arlie V. Bock. Illustrated by Stereopticon.

Light refreshments after the meeting.

HORACE BINNEY, M.D., *Secretary.*

MASSACHUSETTS MEMORIAL HOSPITALS

The monthly meeting of the Surgical Section will be held in the Trustees Room on Friday, January 12, at 12 noon.

Dr. Kenneth K. Day will present a paper on, "Low Back Pain."

RALPH C. WIGGIN, *Secretary.*

SOCIETY MEETINGS, CONGRESSES AND CONFERENCES

January 11—Massachusetts General Hospital, Staff Clinical Meeting at 8:15 P.M. in the Moseley Memorial Building.

January 12—William Harvey Society will meet at 8:00 P.M. in the auditorium of the Beth Israel Hospital, Boston.

January 12—Massachusetts Memorial Hospitals. See notice elsewhere on this page.

January 15—Boston Medical History Club. See notice elsewhere on this page.

January 15, 16, and 17—American Conference on Birth Control will be held at the Mayflower Hotel, Washington, D. C.

January 16—Harvard Medical Society. See notice elsewhere on this page.

January 16—South End Medical Club will meet at 12 noon at the office of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston.

January 16—Boston Medical Library. See notice elsewhere on this page.

January 17—New England Physical Therapy Society. See page 114.

January 18—Boston City Hospital, Staff Clinical Meeting. See page 114.

January 18—New England Hospital for Women and Children. See page 114.

February 7—Annual dinner of the Tufts College Medical School Alumni Association at the Boston City Club, 6:30 P.M.

February 12—House Officers' Association of the Boston City Hospital. Subject: "Forensic Psychiatry". Speakers: Dr. A. Warren Stearns and Dr. Abraham Myerson.

February 16 and 17—The New England Hospital Association is holding its Twelfth Annual Meeting at the University Club, Boston. For details write Dr. A. G. Engelbach, Massachusetts General Hospital, Boston.

April 16-20—The American College of Physicians will hold its Eighteenth Annual Clinical Session in Chicago at the Palmer House. For information write Mr. E. R. Loveland, Executive Secretary, 133-135 South 36th Street, Philadelphia, Pa.

July 24-31—The IVth International Congress of Radiology will be held in Zurich under the presidency of Professor H. R. Schniz. General Secretary Dr. H. E. Walther, Gloriastrasse 14, Zurich.

September 3-6—American Public Health Association. See page 114.

September 4, 5, 6—International Union Against Tuberculosis will be held in Warsaw. For particulars address The National Tuberculosis Association, 450 Seventh Avenue, New York, N. Y.

DISTRICT MEDICAL SOCIETIES

ESSEX SOUTH DISTRICT MEDICAL SOCIETY

February 7—Council Meeting, Boston.

Wednesday, March 7—Lynn Hospital. Clinic 5 P.M. Dinner 7 P.M. Speaker Dr. Frank H. Lahey, Boston. Subject to be announced. Film Electrocardiogram.

Wednesday, April 4—Essex Sanatorium, Middleton. Clinic 5 P.M. Dinner 7 P.M. Speakers: Dr. Elliott P. Joslin and Dr. Howard F. Root, Boston. Subject: "Tuberculosis Complicating Diabetes."

Thursday, May 3—Censors' Meeting, at Salem Hospital, 3:30 P.M.

Tuesday, May 8—Annual Meeting. Salem Country Club, Forrest Street, Peabody. Dinner at 7. Speaker to be announced. Subject to be announced.

RALPH E. STONE, M.D., Secretary.
221 Cabot Street, Beverly, Mass.

FRANKLIN DISTRICT MEDICAL SOCIETY

Meetings will be held on the second Tuesday of March and May at the Weldon Hotel, Greenfield, at 11 A.M.

CHARLES MOLINE, M.D., Secretary.
Sunderland, Mass.

MIDDLESEX EAST DISTRICT MEDICAL SOCIETY

Meetings will take place in March (2nd Wednesday) at Wakefield, and May (2nd Wednesday) at Winchester.

ALLAN R. CUNNINGHAM, M.D., Secretary.
76 Church Street, Winchester, Mass.

MIDDLESEX NORTH DISTRICT MEDICAL SOCIETY

Meetings will be held on January 31, and April 25

T. A. STAMAS, M.D., Secretary.
226 Central Street, Lowell, Mass.

MIDDLESEX SOUTH DISTRICT MEDICAL SOCIETY

February 20—Meeting at the Metropolitan State Hospital, Waltham, 5 P.M.

NORFOLK DISTRICT MEDICAL SOCIETY

January 28—Tentatively Roxbury Masonic Temple, 8 P.M. Continuance of Symposium on Diseases of the Blood. Dr. Dameshek and Dr. Straus.

February 27—Place, time, subject, and speaker to be announced.

March 27—Place and time to be announced. Dr. Edward A. Edwards and Dr. Henry H. Faxon. Symposium on the Treatment of Varicose Veins.

May—Annual Meeting. Place, time and program to be announced.

FRANK S. CRUICKSHANK, M.D., Secretary.
1695 Beacon Street, Brookline, Mass.

NORFOLK SOUTH DISTRICT MEDICAL SOCIETY

February 1—12 noon at Norfolk County Hospital. Stated Meeting. Speaker: Dr. Sara Jordan. Subject: Stomach Ulcers.

March 1—12 noon at Quincy City Hospital. Program by the hospital staff.

April 5—12 noon at Norfolk County Hospital. Speaker: Dr. Elliott P. Joslin. Subject: Diabetes.

May 3—12 noon at Norfolk County Hospital. Annual Meeting. Election of Officers.

N. R. PILLSBURY, M.D., Secretary.
Norfolk County Hospital, South Braintree, Mass.

SUFFOLK DISTRICT MEDICAL SOCIETY

January 31—General Meeting in association with the Boston Medical Library and the Trudeau Society. Speaker: Dr. Lawrason Brown of Saranac Lake.

March 28—Clinical Meeting at the Massachusetts Memorial Hospitals.

April 25—Annual Meeting at the Boston Medical Library. Election of Officers. Scientific Program, titles and speakers to be announced.

The Medical Profession is cordially invited to attend all of these meetings.

JAMES H. MEANS, M.D., Vice-President.
GEORGE P. REYNOLDS, M.D., Secretary,
311 Beacon Street, Boston, Mass.
ALEXANDER S. BEGG, M.D.,
Boston Medical Library.

WORCESTER DISTRICT MEDICAL SOCIETY

All meetings to be held on Wednesdays as follows:

February 14—Dinner and scientific program at the Worcester State Hospital, Worcester, Mass.

March 14—Dinner and scientific program at the Memorial Hospital, Worcester, Mass.

April 11—Open date.

May 9—Annual Meeting. Time and place to be announced later.

ERWIN C. MILLER, M.D., Secretary.
27 Elm Street, Worcester, Mass.

BOOK REVIEWS

A Life Against Death. By KENELM WINSLOW. Published by Lowman & Hanford Company. 292 Pages. Price $3.00.

To the medical reader, the life story of another physician must be dull indeed if it does not call forth memories full of interest. Dr. Winslow's autobiography is far from dull. It is a rambling, disjointed narrative, written entirely from the objective point of view. A series of events is strung along on a thin thread of continuity; one learns what the author did, but never why he did it.

Dr. Winslow's life was not unusual. Born and reared in eastern Massachusetts, he attended the Harvard Medical School, interned at the Massachusetts General Hospital and practiced for a time in Watertown. His descriptions of people and places are vivid, and his tales of yachting adventures are blood-curdling.

After ten years of practice in Watertown, he moved to Seattle. One fails to get a clear picture of his career in that city; in place of that, the reader is told of several amusing or sensational episodes which occurred in Dr. Winslow's practice. The book closes with an account of the author's service in the United States Army, which was a futile and desolate period, as Dr. Winslow himself realizes.

For one who has himself known the institutions and hospitals described in "A Life Against Death," the book makes interesting reading. As a record of a period, it is not without value. A bit more depth, a little more peering beneath the surface of things, would have given it a stability which is now lacking. To use a simile which the author would be sure to understand, we would say that he has hoisted too many light sails, and has not sufficient lead on his keel.

Starling's Principles of Human Physiology. Sixth Edition. Edited and revised by C. Lovatt Evans with the assistance of H. Hartridge. Published by Lea & Febiger, Philadelphia. 1122 Pages. Price $8.75.

Physiology has advanced considerably within the last few years. New physical and chemical methods have been successfully applied. The number of quantitative studies has increased, producing a more accurate appreciation of laws and relations. Yet many facts have been acquired which stand apparently isolated, without any clear correlation with the general knowledge of physiological organization. As a consequence, specialization within the physiological science is more and more apparent. The task of preparing an adequate textbook of physiology is therefore increasingly difficult for a single person or a small number of authors.

In view of these facts, the new edition of Starling's classic deserves warm praise. With minor exceptions the book is as up to date as can be expected. The relative development of the different chapters is in general adequate. Most of the fundamental data and inferences are included and clearly and interestingly presented. The ground covered and the details offered satisfy the needs of medical students. The addition of a short, selected bibliography is especially praiseworthy; the student will find in it a good guide for indispensable further reading.

The first part of the volume, a short summary of some subjects of general physiology, is probably superfluous in a text of human physiology. The functions of autonomic nerves, of smooth muscle and of endocrine glands are perhaps not sufficiently emphasized. Notwithstanding these possible flaws, the book possesses a high pedagogical value and is among the best of modern textbooks of physiology.